CUK-H00624-60.P25687

ISSN 0006-8950

Brain

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A Journal of Neurology

Volume 104 Part I March 1981

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P25687

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Journal of Cerebral Blood Flow and Metabolism

Official Journal of the International Society of Cerebral Blood Flow and Metabolism

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EEG Primer

by R. SPEHLMANN

The main goal of this book is a didactic presentation of clinical EEG and its role in the diagnosis of cerebral disorders. It will be useful for several groups – resident physicians who are in neurology training and need to learn EEG interpretation as part of this training; residents in other fields, interns and medical students who have become interested in EEG; neuroscientists who wish to understand the methods and clinical applications of EEG; EEG technicians who want to gain more insight into the tests they perform; and anyone who wants to find out how clinical EEG is done and what it can do. Explanations start with some simple concepts and build up in steps following an order which generally corresponds with the steps of recording and reading an EEG. The reader can choose the depth at which he wishes to master a topic. Although mainly written for beginners in EEG, those with some experience in EEG will also find the book useful.

CONTENTS: Preface. **Part A: Technical Background.** Introduction. 1. The source of the EEG. 2. Recording electrodes. 3. The EEG machine: Parts and functions. 4. Recording strategy. 5. The product of the recording: The clinical EEG record. 6. Artifacts. 7. Other methods of recording and analysis. **Part B: The normal EEG.** 8. Definition of the normal EEG, relation to brain function. 9. Descriptors of EEG activity. 10. The normal EEG from premature age to the age of 19 years. 11. The normal EEG of wakeful resting adults of 20-60 years of age. 12. The normal sleep EEG adults over 20 years. 13. The normal EEG of adults over 60 years of age. 14. Activation procedures. **Part C: The Abnormal EEG.** 15. Abnormal EEG patterns, correlation with underlying cerebral lesions and neurological diseases. 16. Classification of seizures. 17. Localized epileptiform patterns. 18. Generalised epileptiform patterns. 19. Special epileptiform patterns. 20. Local slow waves. 21. Generalised asynchronous slow waves. 22. Bilaterally synchronous slow waves. 23. Localized and lateralized changes of amplitude: Asymmetries. 24. Generalized changes of amplitude: Symmetrically high and low amplitude. 25. Deviations from normal patterns. 26. The EEG report. Appendix. **Subject index.**

1981 x + 476 pages
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Brain (1981) **104**, 1-20

CEREBRAL DISORDER IN ALCOHOLISM

SYNDROMES OF IMPAIRMENT*

by W. A. LISHMAN

(*From the Institute of Psychiatry, De Crespigny Park, London SE5*)

THE effects of long-continued alcohol abuse on the brain have been taught and retaught in similar fashion for many years. This teaching has only quite recently come under closer scrutiny and it may be interesting to see where newer conceptions appear to be leading us. The large subject matter implied by the title must necessarily be circumscribed; the aim will be to select certain highlights, to see where previously cherished notions must be questioned and where more thorough-going inquiries might usefully be mounted. The focus in effect will be on the cognitive impairments seen in alcoholics and their neuropathological bases.

We start with a simple conception. Namely, that thiamine deficiency in alcoholics can lead to acute Wernicke's encephalopathy, and thereby, if treatment is delayed, to the chronic syndrome of Korsakoff's psychosis in which severe memory impairment is the outstanding mental feature. This is held to account for the majority of alcoholics who suffer serious long-term cognitive impairment. Other alcoholics, not showing Korsakovian features, may also be chronically incapacitated by the accumulation of social handicaps, homelessness, depression, malnutrition and continuous inebriation. A small and uncertain proportion may ultimately suffer from alcoholic 'deterioration' or 'dementia' which presumably depends on more widespread cerebral dysfunction.

This, in summary, is the teaching found in textbooks and passed on since Wernicke and Korsakoff described their striking syndromes in 1881 and 1887. Note how hazy becomes the nosology and how vague the conceptions of ætiology in the latter part of the statement. Chronic cognitive impairment other than Korsakoff's psychosis is very poorly defined. We find the term 'dementia' usually in inverted commas—perhaps an excuse for hinting at a condition without committing oneself too definitely on the issue. We find virtually no attempts at discriminating studies of its clinical or pathological characteristics. This, of course, is consonant with the less than rigorous approach traditionally applied to dementia in all its forms.

Let us examine, therefore, both the status of Wernicke's and Korsakoff's syndromes and the status of more global intellectual impairment in alcoholics.

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* Shorvon Memorial Lecture, delivered at The National Hospital, Queen Square, London, WC1, on May 15, 1980.

The Wernicke-Korsakoff Syndrome

The history of Wernicke's and Korsakoff's conditions, and the way different strands in the picture came to be united, forms one of the most fascinating stories in neuropsychiatry—and not least because clear therapeutic benefit was the product of continuing observations on the subject.

Wernicke described the syndrome that bears his name in his famous text book in 1881. Korsakoff described his six years later in 1887. Each syndrome then followed a distinct historical path for almost half a century before converging on one another. Neither Wernicke nor Korsakoff appreciated the link between the two.

Wernicke reported both the clinical picture and the distinctive pathology of his syndrome. He described the confusional state setting in abruptly, the impairment of consciousness, the ataxia and the ophthalmoplegias. Two of his cases were alcoholics, the third a seamstress suffering from persistent vomiting after sulphuric acid poisoning. The pathology was similar in all three—numerous punctate hæmorrhages symmetrically situated in the grey matter around the third and fourth ventricles and the aqueduct of Sylvius. He attributed it to an inflammatory process and described it as 'polio-encephalitis hæmorrhagica superior', seeing an analogy with poliomyelitis of the cord. Both the clinical picture and its pathological substrate found early and wide acceptance—it was a dramatic and conspicuous lesion-complex, something on which to focus when in all other respects the neuropathology of alcoholism was vague and ill-defined. Later authors emphasized changes in the thalamus and mamillary bodies as well (Gudden, 1896; Bonhoeffer, 1897), but other than this the essential pathology has remained as Wernicke described it.

Korsakoff's psychosis was also speedily accepted as a definite clinical entity. A spate of articles confirmed his description of the characteristic amnesic picture. The pathological basis of the condition was not, however, so readily established. Here it may be useful to trace the earlier history very briefly because it may still have something to teach us.

It is remarkable that for some forty years after Korsakoff's description the pathological basis was almost universally regarded as cortical in location. Korsakoff himself reported changes in cortical vessels along with increased gliosis (Korsakoff and Serbski, 1892). Others agreed, and added chromatolysis of cortical neurons and degeneration of fibres (Cole, 1902; Mott, 1910). The frontal lobes were regarded as especially severely affected. It was not until 1928 that Gamper seriously challenged this view, declaring that the essential lesion lay in the midbrain, around the walls of the third ventricle and in the mamillary bodies, that is in regions similar to those affected in Wernicke's encephalopathy. This did not end the story, however. Carmichael and Stern, reporting cases from the National Hospital in 1931, still described a cortical basis. The cells were primarily affected, with central chromatolysis and a marked and characteristic deposition of lipochrome in the neurons, in neuroglia and around blood vessels. Carmichael and Stern stressed that this pathological picture was virtually an exact parallel of what was seen in patients dying of pellagra, that is of nicotinic acid deficiency. We shall return to this last point later. Marcus, reporting from France also in 1931, similarly located the pathological process in the cortex, particularly the frontal cortex. Parenchymatous degeneration and atrophy could be marked, extending even to loss of normal cytoarchitecture.

Henceforward the two types of pathology continued to be reported in Korsakoff patients, though with cortical lesions gradually yielding pride of place to lesions in the Wernicke location. Some authorities (for example Creutzfeldt, 1928) stressed pathology in both locations. But eventually the authoritative surveys of Malamud and Skillicorn in 1956 and Victor, Adams and Collins, in 1971 stamped a virtually exact parallel between the pathologies of Wernicke's encephalopathy and Korsakoff's psychosis, the lesions differing only in their acuteness or chronicity. Cortical lesions in Korsakoff's psychosis have come increasingly to be ignored or to be mentioned only in passing, and one suspects that intensive studies of cortical regions have latterly become unfashionable. One may note, however, that in Victor *et al.*'s large series convolutional atrophy and ventricular enlargement were obvious on macroscopic examination in no less than a quarter of cases.

Understanding of the pathophysiology of Wernicke's and Korsakoff's syndromes escalated in the 1930s and 40s. Conditions other than alcoholism were noted increasingly to lead to them. It had been known from the earliest accounts that they could occasionally develop against a background of persistent vomiting, and now hyperemesis gravidarum, carcinoma of the stomach, pernicious anæmia and serious malnutrition were established as predisposing causes. A dietary deficiency was already under suspicion on clinical grounds as the unifying feature when experimental work on thiamine deficiency produced immensely persuasive findings. Peters and co-workers (Peters, 1936) showed a focal derangement of pyruvate metabolism, principally in the brain-stem, of the thiamine-deficient pigeon; Alexander and his team demonstrated histological lesions in the pigeon similar in distribution and type to those of human Wernicke's encephalopathy (Alexander, Pijoan and Myerson, 1938; Alexander, 1940). The stage was then set for clinical demonstrations that thiamine could be dramatically effective in relieving the ophthalmoplegias and improving clouding of consciousness in patients with Wernicke's encephalopathy (*see* Jolliffe, Wortis and Fein, 1941), also in ameliorating the picture in some degree in Korsakoff's psychosis (Bowman, Goodhart and Jolliffe, 1939).

Meanwhile the hints, to be found here and there, that Wernicke's and Korsakoff's syndromes might be linked to one another steadily increased. Now that thiamine replacement had reduced the mortality from Wernicke's encephalopathy, greater numbers survived to reveal the chronic amnesic sequelæ. De Wardener and Lennox (1947), for example, reported 52 typical cases of Wernicke's encephalopathy from a prisoner of war camp in Singapore, with clear evidence of memory defects in association with ataxia and ophthalmoplegia; moreover the acuteness of their cases also allowed the amnesic difficulties to respond unequivocally to thiamine in many cases. In Victor *et al.*'s (1971) more recent series from Boston, 186 alcoholic patients survived the acute illness and were observed for sufficient time to assess the presence or absence of Korsakoff's psychosis; the amnesic syndrome followed in 84 per cent.

Other significant developments must not be overlooked. In the 1960s, for example, it was urged that our clinical conception of Wernicke's encephalopathy should be broadened, indeed that it perhaps deserved reappraisal (Cravioto, Korein and Silberman, 1961; Grunnet, 1969). Patients were reported with the classical lesion at autopsy who had died without exhibiting Wernicke's classical signs. The triad of confusion, ataxia and ophthalmoplegia had occurred rather rarely together; hypotension and lethargy were regarded as at least equally characteristic. Comparison of patients dying in the 1930s and the 1960s suggested that the clinical presentation had become less fulminating, perhaps as a result of the wider availability and prescription of vitamins. The lesions at autopsy tended to be more circumscribed in the recent cases, and more often subacute or chronic in nature. Most significant of all, the condition had several times gone unsuspected prior to death.

This latter point has recently been strongly reinforced by Harper (1979). Over the course of four years in Perth, Australia, 51 cases of Wernicke's encephalopathy were diagnosed at autopsy, representing almost 2 per cent of the brains examined in the Royal Perth Hospital. Only 7 of these 51 cases had been suspected during life. The great majority of affected patients were known to be alcoholics, and 10 had died suddenly and unexpectedly. The apparent lack of appreciation of this potentially remediable condition prior to death is striking and rather alarming.

Harper's findings also stress the ease with which the lesion may be overlooked unless histological examination is undertaken. Macroscopically there is often little abnormal to find. The punctate hæmorrhages, once thought typical of the acute stages, were evident to the naked eye in only 5 cases; and the mamillary bodies were macroscopically normal in over a third. A considerable range was encountered in the acuteness or chronicity of the lesions, with the not uncommon conjunction of acute histological changes superimposed on chronic pathology within the same brain regions.

It would seem, therefore, that we have witnessed in turn the emergence of an effective treatment for classical Wernicke's disease; a link forged between this and Korsakoff's psychosis; warnings that Wernicke's syndrome may appear in attenuated and untypical form; and now indications that it remains undiagnosed to a considerable and serious extent.

Is it possible that we should capitalize on this evidence and go even further by accepting *subclinical* forms of the disease? By this I mean accepting that damage may accrue in the Wernicke location without clear clinical indicators to alert us to the process. The lesions may develop insidiously, or more probably in stepwise fashion during episodes of particularly severe thiamine deficiency. The histological evidence as set out by Harper is not discordant with such a proposition, and indeed he raises the possibility of repeated subclinical episodes himself.

What further arguments can be marshalled in favour of the idea? First, we may note certain discrepancies in the prognosis of the amnesic syndrome according to its ætiology. Korsakoff's psychosis of alcoholic origin cannot be predicted to respond well, even when thiamine is administered from the earliest stages. Thus of Victor *et al.*'s (1971) patients a quarter showed complete recovery, half partial recovery, and there was no improvement whatever in the remainder. De Wardener and Lennox's (1947) nutritionally-depleted prisoners, by contrast, showed a generally excellent response of the memory deficits to thiamine. It is tempting to suppose that in the former alcoholic group recurrent attacks of subclinical encephalopathy had often led over years to permanent structural pathology, whereas the prisoners were manifesting their first and only episode. Secondly, one must consider the mode of evolution of chronic Korsakoff's psychosis. Victor *et al.* described an overt attack of Wernicke's encephalopathy as a prelude to the amnesic syndrome in well over 80 per cent of cases; but their patients were largely gathered from two general hospitals in Boston—most indeed were incepted as Wernicke's syndrome then followed through to the Korsakovian development. Clinical experience, by contrast, at least in the UK, suggests that many cases of Korsakoff's psychosis develop their amnesic difficulties without any identifiable history of a Wernicke episode. Many appear to evolve insidiously, in the context of chronic, continuing inebriation. This, however, is an argument that might yet find an alternative explanation, as we shall see later. Finally, one may argue from first principles that a lesion dependent on biochemical changes secondary to vitamin deficiency is rather unlikely to obey an 'all or none' law, especially when the vitamin depletion has been operative for many years; that the lesion should either declare itself totally or fail to develop entirely would seem biologically unlikely.

The issue is not of academic interest alone. If a thiamine-dependent pathology can develop in the Wernicke location long before we suspect it, high potency vitamin replacement should be more often given. The possibility arises, moreover, that not all alcoholics will be equally at risk. Blass and Gibson (1977) propose that an inborn abnormality of the enzyme transketolase may be necessary before thiamine deficiency can lead to the Wernicke-Korsakoff syndrome. If they are correct, attempts at the identification of susceptible subjects among the alcoholic population would warrant a high priority.

Nicotinic Acid Deficiency

Before leaving the topic of vitamins, I wish very briefly to resurrect a partly forgotten syndrome in alcoholics, the so-called 'nicotinic acid deficiency encephalopathy'. This enjoyed something of a vogue in the 1940s, (Cleckley, Sydenstricker and Geeslin, 1939; Jolliffe *et al.*, 1940; Sydenstricker, 1943; Gottlieb, 1944) just when thiamine was proving efficacious for the patients we have been considering so far. Since that time it seems largely to have disappeared from the British and American literature.

The syndrome was catastrophic in development and carried a high mortality. Jolliffe *et al.* (1940) were able to report 150 cases from Bellevue Hospital, New York.

The picture was of stupor or delirium, often with cogwheel rigidity of the limbs and sometimes with grasping and sucking reflexes. Half showed stomatitis or other evidence of a partial pellagrous state, but in others the neuropsychiatric picture was the sole manifestation. Polyneuritis and oculomotor disturbances could be present as in Wernicke's syndrome but this was by no means invariable. Those who survived were commonly left with organic memory deficits (Jolliffe, 1941).

Thiamine was without effect, but nicotinic acid in large dosage produced recovery usually in three to five days. Mortality was drastically reduced by such treatment, from 90 per cent to 14 per cent in Jolliffe *et al.*'s (1940) series.

The justification for recalling the syndrome is that I suspect it has complicated our understanding of the pathology of Wernicke-Korsakoff disease. Carmichael and Stern's (1931) patients, we remember, showed a cortical pathology which they emphasized as typical of pellagra. Some of the clinical protocols of their patients, on re-reading, could fit quite well with the nicotinic acid deficiency syndrome. It may be, therefore, that we have often confounded two vitamin deficiency encephalopathies—of thiamine and of nicotinic acid—usually occurring together but sometimes appearing in isolation. Deficiencies of single vitamins are rare. But we have already seen that genetic predilection may be important before thiamine depletion leads to cerebral pathology, and similar factors could govern the neuropathic effects of other vitamins too. The long history of uncertainty about cortical *versus* subcortical pathology in Korsakoff's syndrome could conceivably have depended, in part, on these two routes to its development.

Nowadays, of course, high potency vitamin therapy almost invariably consists of multiple vitamin replacement. Parentrovite injections in the UK, and Solu-B or Bejectal in the USA, contain ample nicotinamide in addition to thiamine. We have little need clinically to pause, therefore, and consider whether we are treating a thiamine or a nicotinic acid deficiency syndrome. Multiple vitamin therapy was adopted as a routine from the 1950s onwards, which is the probable explanation for the demise of the nicotinic acid deficiency syndrome in the UK and the USA. I have been interested to learn, however, that it is still evident in other countries. Dr M. S. Kayatekin has informed me of three alcoholic patients seen recently in Turkey, with severe and prolonged confusion developing within a few days of recovery from delirium tremens. Treatment with parenteral thiamine, riboflavine and pyridoxine was without effect until nicotinic acid was added in very large dosage; the organic mental syndrome then cleared promptly and completely in all cases.

Alcoholic 'Dementia'

Turning now to the vexed and troubled subject of alcoholic dementia we can perhaps again look with profit at history. Early accounts from mental hospitals regularly spoke of such dementia; indeed in the latter part of the 19th century it was considered difficult to distinguish between it and general paresis. In the first volume of *Brain*, in 1878, we find Dr Lawson of the Wonford House Lunatic Hospital, Exeter, foreshadowing Korsakoff by describing circumscribed memory deficits in alcoholics, but then proceeding to describe a different class of case in which mental dulling led on to global dementia. Maudsley (1879), in *The Pathology of Mind*, noted childish understanding, blunted moral sense and weak will-power; if drinking was not arrested the patient became 'completely demented, his mind being thoroughly disorganized . . . he resembles not a little in mental symptoms a person who is in the last stage of senile dementia'. Bevan Lewis (1889), from the Wakefield asylum wrote that 'the functional disturbances described as present in acute alcoholism become interblended (if drinking be still persisted in) with symptoms indicative of *structural change*, the injurious action of the stimulant becomes stamped upon the organism . . . The chief indications of such organic change are advancing and *persistent mental enfeeblement* . . . the faculties of attention, of judgement, and of comparison suffer; and memory is especially implicated. The finer sensibilities are worn off; the subject is less impressionable and sympathetic, less charitable, as well as more narrowed and selfish in his desires, his altruistic sentiments rapidly declining . . . the whole moral nature undergoes a profound and serious change.' Similar descriptions from the 19th century literature abound.

We find, however, that after Korsakoff's psychosis became widely recognized the term 'dementia' appears less and less often. Clouston still uses it in 1904, but Mott does not in 1910. The authorities are eager to describe the new Korsakoff syndrome, and one is led to assume that the former dements had been improperly labelled.

But what, I wonder, is the true situation? Has alcoholic dementia really disappeared? Was it always in reality a Korsakoff syndrome? Can alcoholics who escape this distinctive complication truly escape substantial damage to their brains? In this connection we must take care not to think of chronic hospital populations alone. What is the cerebral status of the 'skid row' alcoholics who drift about our city centres and lodging houses? Edwards' noteworthy survey (Edwards, Hawker, Williamson and Hensman, 1966) showed that only 20 of 51 skid row subjects had at any time been admitted to psychiatric care.

Thus we lack adequate epidemiological information. Of alcoholics coming forward for treatment we sometimes find a substantial proportion labelled as demented, for example, some 8 to 9 per cent of 1000 consecutive attenders at an alcoholism clinic in Melbourne, Australia (Wilkinson, Kornaczewski, Rankin and Santamaria, 1971; Horvath, 1975). But again we have insufficient information to decide whether a truly global dementia was afoot.

The problem can be approached from a different aspect, by seeing how often alcoholism is considered a likely operative factor among demented patients generally. Three surveys, from England, Australia and America, are shown in Table 1. Alcohol has clearly been suspected as a cause in a substantial proportion of dements—approximately as frequently as multi-infarct dementia. Here, however, the ætiological relationship is merely suspected, by no means confirmed. We may conclude at the very least, however, that some global affection of intellect, sometimes severely developed, warrants serious consideration as a possible complication of alcoholism.

TABLE 1. SURVEYS OF CAUSES OF DEMENTIA AMONG PATIENTS IN HOSPITAL FOR INVESTIGATION

	Total patients	*Dementia confirmed*	*Unknown cause (?Alzheimer's)*	*Multi-infarct*	*?Alcoholic dementia*
Marsden and Harrison, 1972	106	84	48 (57 %)	8 (9.5 %)	6* (7 %)
Smith, Kiloh, Ratnavale, and Grant, 1976	100	81	36 (44 %)	12 (15 %)	17** (21 %)
Freemon, 1976	60	54	26 (48 %)	5 (9 %)	4*** (7 %)

* So labelled when history of prolonged excessive alcohol consumption associated with one of: peripheral neuropathy, cerebellar ataxia principally affecting gait, or cerebellar atrophy on AEG. ** Alcoholism considered to 'contribute' to dementia. *** Chronic alcoholism associated with the dementia and mild to moderate cortical atrophy on AEG.

Psychologists have certainly highlighted the cognitive abnormalities that can emerge with appropriate testing, even in seemingly 'intact' alcoholics and persisting well after the 'drying-out' period. Such observations now form a large part of the clinical psychological literature which cannot be dealt with in detail here. The topic has been extensively reviewed by Parsons (1977) and Tarter (1980). But clearly, even when performance is adequate on standard intelligence tests, difficulties can be shown with many aspects of new learning, with visuospatial functions, and such matters as abstract thinking and psychomotor speed. Patients handicapped in these respects have been shown to be especially liable to continuation of drinking and to be resistant to rehabilitation (Gregson and Taylor, 1977). We are still a long way, with such impairments, however, from what we could term 'dementia'.

Despairing of clinical observational evidence we can turn to examination of the brain. The pathologists, frankly, disappoint us. There is no consensus or consistency in their observations. Some report cortical atrophy but many do not. Some find neuronal degeneration and loss, patchy and diffuse, whereas others declare the cerebral hemispheres substantially normal. Lynch (1960), himself describing cortical and white matter changes, attributed the negative reports to a waning of neuropathological interest in the cortex of alcoholics. The accent of pathological inquiry had become decidedly focal, on the Wernicke-type lesion and more recently, on the cerebellum. One can certainly understand the tendency to concentrate on lesions that will be definite, rewarding, and lead to a clear neuropathological diagnosis. Lynch also points out how inherently difficult it is to chart changes, degenerations and loss of components in such a complex crowded area as the cortex. Even in the advanced unequivocal dementias, such as Alzheimer's disease, we rely more on phenomena such as plaques and tangles for making a diagnosis than on evaluating changes in the neuronal population.

Even at the macroscopic level, however, there is no unanimity. Cerebral atrophy, mild or moderate in degree, was reported in a high proportion of Courville's (1955) chronic alcoholics, in half of Neuberger's (1957) and all of Lynch's (1960). Numerous other reports, however, do not find it or do not comment on it. The possibility occurs that a mild or moderate degree of atrophy may sometimes have become obscured by terminal brain swelling, or the œdema associated with recent intoxication or delirium tremens. Many reported autopsies are from coroners' examinations, but unfortunately clinical details of the immediate ante-mortem status are rarely given.

Courville (1955) was perhaps the most vigorous proponent of cerebral atrophy, describing alcoholism as the most frequent cause of brain shrinkage in the fifth and sixth decades of life. He described fairly uniform atrophy, maximal over the dorsolateral frontal regions, and extending to pre- and post-central gyri and into the superior parietal lobule. Sections showed widened sulci, a narrowed cortical ribbon, and enlargement particularly of the anterior horns of the lateral ventricles. Histological examination was said to show cell loss and degeneration, and nerve fibre disintegration with dissolution of myelin sheaths.

Meanwhile a steady trickle of reports has often indicated that 'atrophy' may be commoner than expected on air encephalography. This investigation was of course hard to justify except on small and selected groups of subjects, and the finding has accordingly been viewed with some reserve. Certain studies are impressive, nevertheless, such as those of Haug (1968) and Brewer and Perrett (1971), with between half and three-quarters of subjects showing cortical changes or ventricular enlargement, and often when unexpected on clinical grounds. Brewer and Perrett's group of 33 heavy drinkers showed high correlations between severity of cortical changes and measures of cognitive impairment on psychological testing.

Lereboullet, Pluvinage and Amstutz (1956) were able to assemble 77 alcoholics with 'indubitable atrophy' on AEG, after rigorously excluding those with head injuries or other known contributory causes which might have accounted for it. The frontal lobes were once more particularly affected. Forty were under 50 years of age and all but 5 under 60. Twelve patients went on to autopsy and close correspondence was observed between radiological and post-mortem findings. A puzzling feature, emphasized by the authors, was the lack of correlation between the degree of atrophy shown and the patients' clinical status—those with severe intellectual and memory impairments could show the same degree of atrophy as those responding favourably and returning to work. Lereboullet *et al.* (1956) considered that nutritional factors might be the principal cause—according to drinking pattern, specific aspects of nutritional lack, or perhaps individual susceptibilities, the deficiency could declare itself abruptly as a Wernicke's encephalopathy or evolve surreptitiously as atrophy. A direct toxic action of alcohol must, of course, also be considered as a possible ætiological factor. Long-term alcohol administration in the experimental animal has been shown to have severe effects on neurons and their processes, even in the absence of any malnutrition (Riley and Walker, 1978).

TABLE 2. CAT-SCAN STUDIES IN ALCOHOLICS

	Sample	*Findings*
Fox, Ramsey, Huckman and Proske, 1976	12 patients with liver disease	Enlarged ventricles, marked in 4 cases
Carlen, Wilkinson and Kiraly, 1976	15 patients with impaired mental function	Cerebral atrophy in all
Epstein, Pisani and Fawcett, 1977	46 patients (retrospective)	Atrophy 61 per cent
Cala, Jones, Mastaglia and Wiley, 1978	26 patients	Atrophy 73 per cent. Severe in 50 per cent
von Gall, Becker, Artmann, Lerch and Nemeth, 1978	60 patients	Pronounced atrophy 75 per cent
Bergman, Borg, Hindmarsh, Ideström and Mützell, 1979	106 consecutive patients	Cortical changes 60 per cent Enlarged lat. ventricles 33 per cent Enlarged 3rd ventricle 48 per cent
Ron, Acker and Lishman, 1979	49 'non-impaired' patients	Cortical changes 55 per cent Enlarged ventricles 35 per cent

CAT scanning has now allowed more thorough-going surveys of alcoholic patients. Table 2 summarizes reports to date, again revealing a high incidence of changes considered significant. These are from varied groups of patients, some with obvious brain damage and some without. Unfortunately few have examined healthy non-alcoholics for accurate control comparisons.

At the Institute of Psychiatry a CAT-scan survey is underway and results are available on 100 male alcoholics and 50 healthy controls of equivalent age. The scans are measured and rated 'blind' for comparison with one another. This work is carried out by Drs Maria Ron and William Acker (reported in more detail in Lishman, Ron and Acker, 1980). The alcoholics are from the Bexley Hospital alcoholism unit under the care of Dr K. Shaw who is collaborating on the project. We have excluded any patients in whom one might have suspected brain damage from any cause whatsoever. Certainly none had the least suspicion of Korsakoff's psychosis. Scans were carried out only after a thorough 'drying-out' period of several weeks (mean thirty-four days). The ages of the patients ranged from 22 to 63 years (mean 43.5 years).

Sulcal widening on the top-most cuts was graded on a 4-point scale, judging each scan against pre-agreed norms (fig. 1). Sylvian fissure widening and inter-hemispheric fissure widening were graded on 3-point and 2-point scales (figs. 2 and 3). Ventricular size was measured by planimetry (on the two cuts showing the maximum amount of ventricle) and expressed as a proportion of total cranial area within these slices.

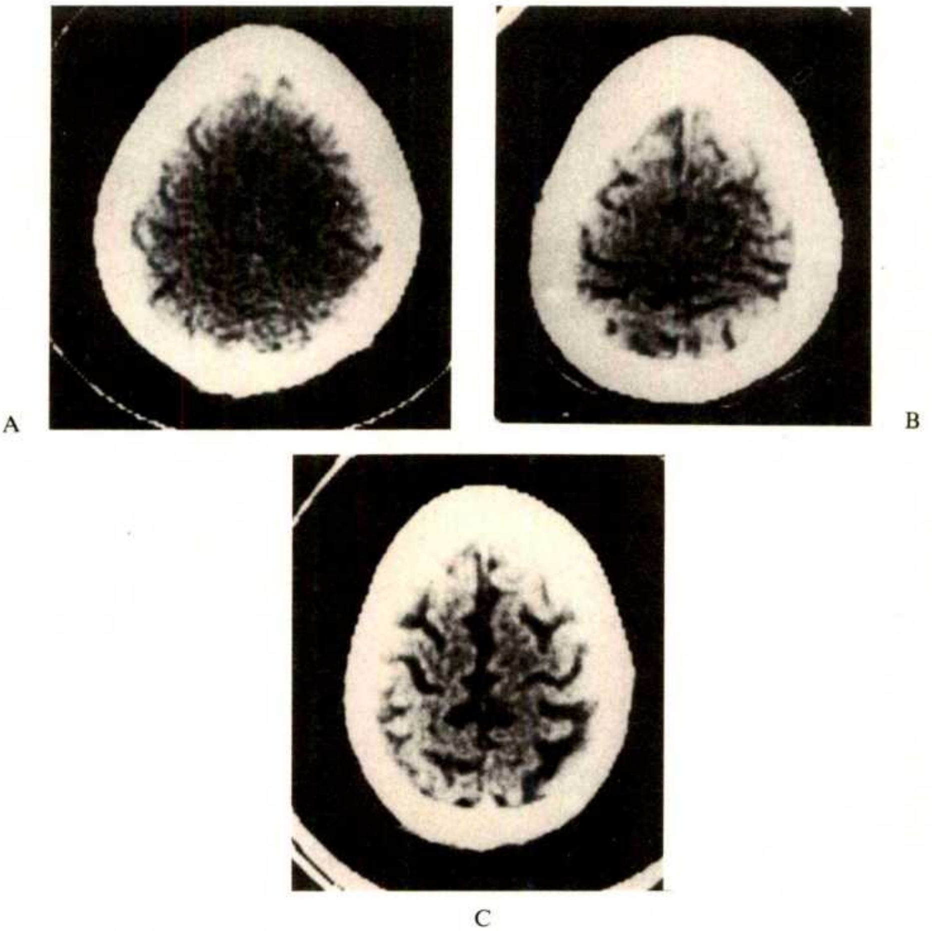

FIG. 1. Grading of sulcal widening: samples used for allocation to grades 0 to 3. A, upper limit of 0. B, upper limit of 1. C, upper limit of 2. Distribution of grades among alcoholic and control subjects are shown in Table 3.

Table 3 shows the highly significant differences that emerged on all indices of cortical shrinkage between our groups of alcoholics and controls. Over 40 per cent of alcoholics, for example, have grades 2 or 3 of sulcal widening compared to only 4 per cent of controls. The mean ventricle/brain ratio is approximately half as large again in the alcoholics as the controls.

Further aspects of the data of possible interest in the present context are these: psychometric testing in this superficially 'intact' group of patients showed some significant correlations between severity of changes in the CAT scan and severity of impairment on certain tests, but concordance was not obvious or extensive.

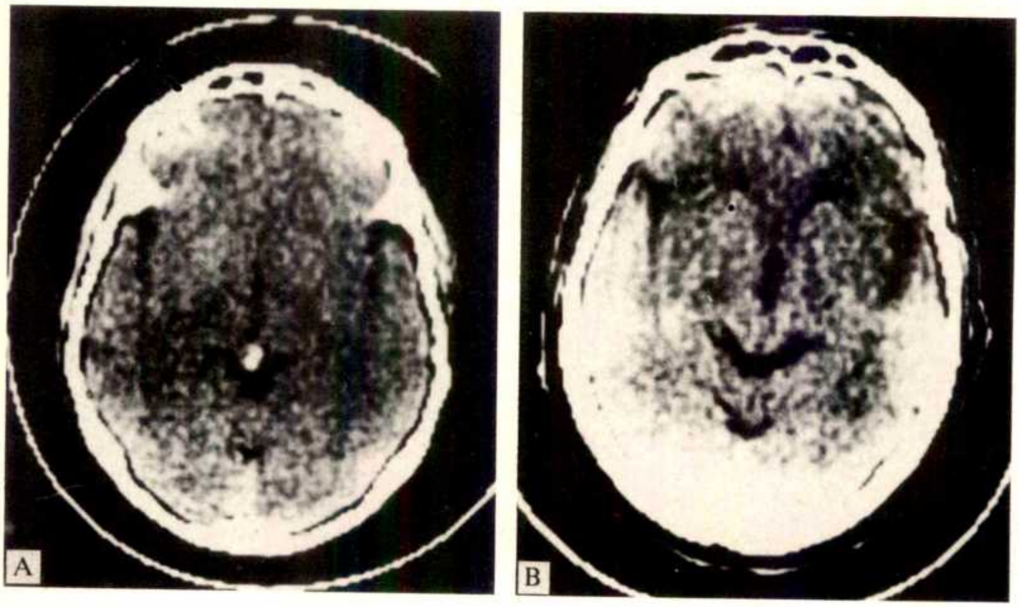

FIG. 2. Grading of Sylvian fissure widening: samples used for allocation to grades 0 to 2. A, upper limit of 0. B, upper limit of 1. Distribution of grades among alcoholic and control subjects are shown in Table 3.

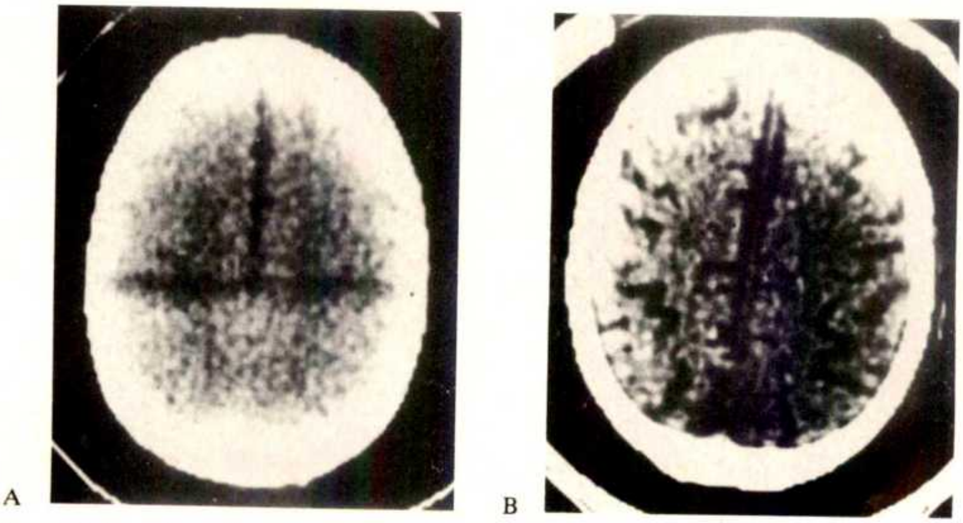

FIG. 3. Grading of interhemispheric fissure widening: samples used for allocation to grades 0 to 1. A, upper limit of 0. B, Grade 1. Distribution of grades among alcoholic and control subjects are shown in Table 3.

TABLE 3. CAT-SCAN FINDINGS IN ALCOHOLICS AND NON-ALCOHOLIC CONTROLS

	Alcoholics (*n = 100*)	*Controls* (*N = 50*)	
Mean age	43.5 yrs	41.5 yrs	
Sulcal widening			
Grade 0	32	37	$\chi^2 = 29.8, P < 0.001$
1	24	11	
2	29	2	
3	14	0	
Sylvian fissure widening			
Grade 0	51	44	$\chi^2 = 20.7, P < 0.001$
1	35	6	
2	14	0	
Interhemispheric fissure widening			
Grade 0	71	46	$\chi^2 = 7.4, P < 0.01$
1	29	4	
Ventricle/brain ratio			
Mean	9.6	6.2	$t = 8.2, P < 0.001$
(SD)	(3.0)	(2.0)	

Significant differences emerged between alcoholics and controls below the age of 40 years, as well as in older subjects. Amongst older subjects both cortical shrinkage and ventricular enlargement were more severe the shorter the interval between cessation of drinking and scanning, suggesting some slight recovery towards normal appearances with abstinence lasting for several weeks or months. Even with follow-up of a group of subjects after twelve months of abstinence, however, the majority of scans remained demonstrably abnormal.

Synthesis and Conclusions

How are we to synthesize the numerous, often puzzling and conflicting observations reviewed so far? Perhaps the time is not ripe to do so, but an attempt can always be made.

We have, first, the indication that a Wernicke-type pathology may be commoner than suspected in the brains of alcoholics, and the implication, admittedly from indirect evidence, that it may sometimes develop surreptitiously without clinically obvious episodes. We have evidence, in addition, that a high proportion, even of quite young alcoholics, have significant cortical shrinkage and ventricular dilatation on the CAT scan, persisting despite abstinence for a year or more, though possibly slowly receding. We have noted that a cortical component to the pathology may have been underplayed in recent accounts of chronic alcoholism and of Korsakoff's syndrome. And that widespread affections of intellectual function, sometimes subtle, sometimes severe, may have failed to attract due attention from present-day clinicians.

I think the sum total of evidence points to the possibility that we have been too far seduced by the Wernicke-Korsakoff syndrome and by rigid conceptions of its pathological substrate; and that we have tended as a result to overlook cortical damage in alcoholics, both clinically and at autopsy.

Two strands can be discerned in this turn of events: the attraction, both clinically and pathologically, of the clear phenomena of the Wernicke-Korsakoff syndrome, and the off-putting ring to the term 'alcoholic dementia'. Each may have contributed to our being side-tracked from the true complexities of alcoholic brain damage.

TABLE 4. COMPARISON OF PATIENTS WITH 'KORSAKOFF'S SYNDROME' AND 'ALCOHOLIC DEMENTIA'

	Korsakoff's syndrome		*Alcoholic dementia*
	Acute onset	*Gradual onset*	
Number	25	17	13
% Female	36 %	65 %	54 %
Age	52	62	60
Duration of symptoms	3 w	12 m	13 m
Improved subsequently	3/21 = 14 %	8/12 = 67 %	7/11 = 64 %

After Cutting, J. (1978) *British Journal of Psychiatry*, 132, 240.

With regard to the first, the over-emphasis on Wernicke-Korsakoff psychosis: this emerged clearly in Cutting's (1978) retrospective survey of patients admitted to The Maudsley Hospital. Fifty alcoholics had been labelled as Korsakoff's psychosis and 13 as 'alcoholic dementia'. But when the former were subdivided into those with relatively acute and gradual onset the results were as shown in Table 4. The gradual-onset Korsakoffs were in reality much closer to the alcoholic dements on a number of features—female preponderance, age, and duration of symptoms. Moreover about two-thirds improved subsequently (to the extent of being capable of living independently for the greater part of the follow-up period) which was rare among the acute-onset Korsakoffs. Table 5 shows psychological test profiles in the groups. The acute-onset Korsakoffs had a reasonable level of general intelligence as expected; the gradual-onset group and the 'dements' showed global impairments across many functions. The similarity between the latter two groups is again striking. Thus it would seem that the intellectually damaged alcoholics admitted to The Maudsley Hospital fall into two roughly equal groups: along with 25 cases of Korsakoff's psychosis we have 30 with more global intellectual defects. Yet 17 of these 30 had been given a firm discharge diagnosis of Korsakoff's psychosis. Perhaps this is in part where the alcoholic dements of the past century have been buried!

TABLE 5. PSYCHOMETRIC TEST RESULTS IN PATIENTS WITH 'KORSAKOFF'S SYNDROME' AND 'ALCOHOLIC DEMENTIA'

	Korsakoff's syndrome		*Alcoholic dementia*
	Acute onset	*Gradual onset*	
No. of patients	21	15	8
Wechsler Adult Intelligence Scale			
Mean IQ	101	87	88
Vocabulary	12.2	8.3	8.5
Similarities	8.2	5.7	5.7
Digit span	11.0	7.6	7.0
Picture completion	9.2	6.6	6.0
Object assembly	7.7	5.5	4.7
Digit symbol	4.9	3.4	4.0

After Cutting, J. (1978) *British Journal of Psychiatry*, 132, 240.

The second strand—the unacceptability of the term 'alcoholic dementia'—is easily understood. The majority of Cutting's patients, just described, were not apparently demented in a formal extensive sense. Though impaired on psychometry they did not deteriorate progressively on follow-up, but in fact fared much better than those with true Korsakoff's psychosis. We need, I think, a more gentle clinical conception of global cerebral affection in alcoholic patients. The term 'accelerated psychological deterioration' is favoured by Cutting. Bennett (1960) coined the term 'intermediate brain syndrome' when he astutely drew attention to patients who fell between the extremes of acute reversible intoxication and fixed structural brain defect. But whatever term is used I think we must recognize that a great number of alcoholics—perhaps the majority of severe alcoholics—impair their brains quite early on in their drinking careers. This impairment is structurally demonstrable, on the CAT scan at least, but appears to remain relatively benign over very many years, benign in the sense of being non-progressive beyond a certain stage, affecting brain function only moderately, and being potentially reversible in some degree with abstinence. A balance may be constantly being restruck between degenerative and regenerative influences in the neurons and their processes. As the alcoholic gets older, however, this affection will couple readily with other pathologies—those of ageing, trauma, vascular changes, hepatic dysfunction—to lead to more serious and irreversible change. A permanent loss of available functioning neurons may gradually build up, so that by late middle age a proportion are now earning the full term 'alcoholic dementia'.

With two possible covert pathologies, moreover, one must wonder about their interactions. Could it be that cortical change and change in the Wernicke region are sometimes operative together in leading to clinical defects? Could this account for the long history of confusion concerning the pathology of 'Korsakoff's syndrome'?

We seem at last on firm ground in attributing the amnesic difficulties of Korsakoff patients to thalamic and hypothalamic pathology, but may cortical changes still influence other aspects of the picture—the indifference, the lack of insight, even the confabulation? In the converse respect, could it be an unsuspected Wernicke pathology that occasionally converts the relatively benign CAT scan changes into something more disabling and pernicious?

These suggestions, if substantiated, would carry implications for clinical practice. Should high potency vitamin preparations be given for a wider range of clinical disorders in alcoholics, and be more often used prophylactically than at present? Should transketolase studies attempt to identify especially susceptible subjects? Should we search routinely for indications of cortical dysfunction in alcoholic patients, and intensify efforts to ensure prolonged abstinence when these are present? Is the traditional group therapy orientated approach optimal for all alcoholics, or are some too impaired psychologically to benefit from this? Should prolonged hospital stay and a behavioural approach to the addiction be specially prescribed in certain instances?

Questions for the Future

The various ideas discussed could easily be multiplied in the present state of knowledge. They are presented more to indicate where future enquiries might lie than as clear distillations of evidence. But I think they represent testable hypotheses.

We need now to attempt to make firm progress on Wernicke's and Korsakoff's observations. To determine, for example, through clinicopathological inquiry, the true status regarding a subclinical Wernicke's pathology. It will be no small task to study brains of alcoholics at autopsy whose ante-mortem psychological functioning has been adequately charted. We surely need a discriminating and properly 'controlled' analysis of cortical pathology in alcoholics, both in those with and without Korsakovian manifestations. The biochemical and the morphological bases of the ubiquitous shrinkage revealed by CAT scanning are clear targets for research.

On the clinical front we need to know much more about the natural history of this shrinkage and its clinical associations. And we need research, prospective where possible, to clarify the range, incidence, and mode of evolution of serious psychological impairments in alcoholic populations. Our conceptions of alcoholic deterioration and dementia require to be tightened, and to be set against equally rigorous criteria where Korsakoff's psychosis is concerned.

Perhaps above all we should seek to clarify not just cognitive but also behavioural changes broadly in alcoholics in relation to their cerebral pathology. Impulse control, loss of tolerance, drastic change in interpersonal relationships and in life goals—these will perhaps deserve new formulations against new knowledge of brain malfunction. Such issues are difficult targets for research, but we now have some of the necessary techniques to allow physiology and pathology to take their places alongside the study of psychodynamic and social processes in unravelling the determinants and consequences of this extremely common addiction.

ACKNOWLEDGEMENTS

I acknowledge with gratitude the help accorded during the preparation of this lecture by Professor J. A. N. Corsellis, Dr John Cutting, Professor Griffith Edwards and Dr Maria Ron. The research in progress is supported by the Medical Research Council.

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(*Received June 5, 1980*)

Brain (1981), **104**, 21-49

LEXICAL OR ORTHOGRAPHIC AGRAPHIA

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INTRODUCTION

NUMEROUS studies of alexia have already been carried out in the framework of the information-processing approach (*see* especially Marshall and Newcombe, 1973; Shallice and Warrington, 1975, 1980; Patterson and Marcel, 1977; Saffran and Marin, 1977; Beauvois and Dérouesné, 1979*a*; Dérouesné and Beauvois, 1979; Morton and Patterson, 1980). But, whereas the information-processing analysis of writing in normal adults has now begun (Morton, 1980; Ellis, 1979), there have, to our knowledge, been no such studies on patients with agraphia. Indeed, the more recent studies on agraphia have aimed, as in the past, either to establish the existence of the syndrome of pure agraphia (Dubois, Hécaen and Marcie, 1969; Assal, Chapuis and Zander, 1970; Kinsbourne and Rosenfield, 1974; Aimard, Devic, Lebel, Trouillas and Boisson, 1975); to study the link between writing-impairment and other language-impairments (Hécaen, Angelergues and Douzenis, 1963; Dubois, 1977; Basso, Taborelli and Vignolo, 1978; Wapner and Gardner, 1979; Marcie and Hécaen, 1979); or to study the link between the existence of agraphia and a particular location of lesion (Hécaen and Angelergues, 1966). In this paper we have attempted to study a case of agraphia with an information-processing approach, and in relation to comparable recent studies on alexia.

In the last few years several neuropsychological studies have provided evidence for the existence of at least two reading processes: one lexical, one non-lexical or phonological. In the phonological reading process, reading is assumed to be mediated by phonological processing, that is, by the use of grapheme-phoneme correspondence. In the lexical reading process, reading is assumed to be carried out by means of lexical or semantic processing. The neuropsychological evidence for the existence of these two reading processes is the contrast between two kinds of alexia. Patients suffering from *surface dyslexia* (Marshall and Newcombe, 1973; Shallice and Warrington, 1980), especially the cases of Kremin (1979) and Deloche, Andreewsky and Desi (1980), cannot read orthographically irregular words correctly, whereas they can read pronounceable non-words well enough. Their reading performance seems therefore to be characterized by impairment of the lexical reading process and relative preservation of the phonological reading

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process. Conversely, patients suffering from *deep dyslexia* (Marshall and Newcombe, 1973), or *phonemic dyslexia* (Shallice and Warrington, 1975), and above all those exhibiting the 'purer' syndrome that we have called *phonological alexia* (Beauvois and Dérouesné, 1979*a*; Dérouesné and Beauvois, 1979), are incapable of reading non-words and can read words well enough, without being affected by their orthographic irregularity. Their reading performance seems therefore to be characterized by impairment of the phonological reading process and relative preservation of the lexical reading process.

Might it be possible to find the same elements in writing? Is it possible to find two dissociable writing processes, one phonological, one lexical? The phonological writing process would deal with the conversion of phonemes into graphemes by using the rules of phoneme-grapheme conversion. For instance, according to these rules in French the phoneme /o/ can be written either O, or AU, or EAU, or even, in certain sequential positions AUX, EAUX, OT, AUD, etc. . . . The lexical writing process would deal with the translation of a heard, or spoken, or thought word into a written word, that is to say with the fact that in a particular word the phoneme /o/ *must* be written EAU; obviously the orthographically irregular words would be dealt with by this lexical process. Is it possible to find two kinds of agraphia corresponding to a disturbance of each of these processes just as it has been possible to describe two kinds of alexia: phonological agraphia and lexical agraphia? We think this is indeed possible, and report here one of the two dissociations, that is, a case of lexical or orthographic agraphia.

CASE SUMMARY

The patient, R.G., was a right-handed man, born in 1912. In 1974 he had been operated upon for a left parieto-occipital angioma. The neurological and neuropsychological picture remained unchanged from 1975 to 1979, and have been described previously (*see* Beauvois, Saillant, Meininger and Lhermitte, 1978; Beauvois and Dérouesné, 1979*a*, *b*; Dérouesné and Beauvois, 1979). Three points must be emphasized:

(1) The patient's IQ remained in the average range. Therefore his writing impairment is not likely to be attributable to intellectual deterioration or confusional state (Chedru and Geschwind, 1972).

(2) There is strong evidence to suggest that the patient's spelling ability was good before his illness. His educational level was relatively high. He had passed the *Brevet Elémentaire*, an examination taken after four years of secondary school. At the time, that is, fifty years ago, success in this examination necessitated good spelling capacity. He used to read for at least two hours a day. His professional activities involved extensive letter-writing. He was an agricultural machinery sales manager in charge of twenty representatives. He had to write regularly to his representatives, suppliers and buyers and to compose administrative reports. We have been able to examine two handwritten examples of his commercial correspondence, dated 1971. They contain numerous orthographically ambiguous words (as they will be defined in the next section) which were all spelled correctly.

(3) With the exception of the three specific deficits that have been particularly studied (bilateral tactile aphasia, phonological alexia and lexical agraphia; *see references above*), the patient's expression and comprehension were normal.

NEUROPSYCHOLOGICAL STUDY

The investigation of the writing impairment was threefold. First, we sought evidence of disturbance of the lexical writing process with preservation of the phonological writing process. Then we tried to locate the level of the processing whose impairment was responsible for the agraphia. Finally, we studied the relationship between reading and writing, which, in this patient, is of great interest.

The study of writing was effected in two phases. The first data were collected in 1975–6, at the time that the patient's reading capacity was tested. The investigation was not then particularly designed to test the patient's spelling capacity. Therefore the analysis of these data is a *post hoc* analysis. The corpus included orthographically ambiguous words but only four orthographically irregular words. Other experiments were designed later in order to provide a more precise test of the effects of orthographic ambiguity and irregularity in writing and in spelling aloud. They were carried out in 1979 (indicated by '1979' in brackets). Unfortunately the patient's physical state suddenly deteriorated so that it was not possible to finish these experiments: writing to dictation of words with different degrees of ambiguity could not be carried out. This is why we have given the results both of 1976 and of 1979. As will become clear below, the impairment remained unchanged from 1976 to 1979.

I. Impairment of the Lexical Writing Process without Impairment of the Phonological Writing Process

A patient with such a condition would be expected to write non-words correctly but not orthographically ambiguous or irregular words; his writing of such words should be phonetically but not orthographically correct.

Since the principal aim of the experiment was to study in writing the difference between lexical processing and phonological processing, two kinds of spelling rules were distinguished among those reported by Gak (1976). The first kind, called *phoneme-grapheme (PG) conversion rules* consist of all the spelling rules that do not refer to the word, that is, that permit us to write non-words, including those concerning the phoneme sequential position; for example, '/z/ is written S between two vowels and Z elsewhere' is a PG conversion rule. The second kind, called *lexical or orthographic rules*, refer to the word, to its composition, its possible derivational forms, its etymology, etc.; for example, '/s/ must be written S between two vowels if the word includes the prefixes A, ANTI, AUTO, etc.... as in the word ASYMETRIE' is a lexical rule because its application depends upon a morphemic segmentation; in the same way, 'terminal /ɛʀ/ must be written ER in words that originate from English', is a lexical rule.

An *ambiguous* word is a word that, in accordance with the rules of PG conversion, can be written in several ways. Its particular spelling depends on lexical rules. For example, in French, in accordance with these rules, CHATEAU could be written too, CHATO, CHATAU, CHATAUX, CHATOT, etc....

An *irregular word* is a word containing a phoneme-grapheme mapping which is exceptional in French (that is, almost unique). For example, in the French word FEMME, /fam/, the phoneme /a/ is irregularly written E.

(1) *Writing non-words to dictation.* Virtually all non-words, even the long or complex ones, were perfectly written to dictation (*see* Table 1). In addition, the way they were correctly written is of interest. Most of them (71 per cent) were written in

TABLE 1. WRITING OF NON-WORDS TO DICTATION. PERCENTAGES OF CORRECT RESPONSES

Tests	*Examples*	*Results* %
40 two-phoneme syllables	zi, al, oi	100
20 three-phoneme syllables	ful, raʃ	95
10 five-phoneme non-words	orfoi, makti	100
20 six-phoneme non-words (CVCVCV)	ziguno, nozija	100
20 complex four-phoneme syllables (CCVC)	drak, vrim, klal	100
110 non-words		99

the most economical way. For example, most often /o/ was written O and not EAU, /f/ was written F and not PH, /ɛ̃/ was written IN and not EIN or AIN; few mute letters or double letters were used. However, it occasionally happened that a syllable which could be written simply was written in a complex manner (for instance, /vɛk/, which can be written VEC or VEK was written VAIQUE); that mute H and mute E and double letters were used (for instance, /yf/ → HUF; /Ryb/ → RUBE; /zekona/ → ZECCONA). The patient always took into account the sequential position of graphemes: (a) double and mute letters were always used in accordance with phoneme-grapheme conversion rules (for instance, a double consonant was placed between two vowels; a mute E was added at the end of a non-word when it finished by the phoneme /b/ or /d/); (b) an identical phoneme was transcribed in different ways, depending on its sequential position (for instance, /z/ was written S when it was possible, that is, when it was placed between two vowels, as in LASE, and was written Z when it was necessary, that is, at the beginning of a non-word, such as ZECONA; /s/ was written C when possible, that is, in front of I or E, as in CID, and S when necessary, as in RISPE).

(2) *Writing ambiguous words to dictation.* The degree of orthographic ambiguity of a word was evaluated by the number of its mute letters and its ambiguous phonemes. An ambiguous phoneme is a phoneme which, in accordance with phoneme-grapheme conversion rules, can be written in several different ways. In that sense, in French, /o/ seems to be ambiguous and /a/ to be non-ambiguous. But, in addition, it is necessary to take into account the frequency of phoneme-grapheme mappings. As a matter of fact, if the non-word /bitiri/ has to be written to dictation, one will probably not write it BYTYRY, but BITIRI, because in French the phoneme /i/ is written I much more frequently than Y; and in the same way, if the non-word /tofo/ has to be written to dictation, one would certainly not write it TEAUPHAU; it is much more probable that one will write it in the most frequent (and economical) way, which is TOFO. Consequently, it was decided that a phoneme was orthographically ambiguous when, in a particular word, and in accordance with phoneme-grapheme conversion rules, it has to be written *not* in the most frequent

way. For example /o/ was considered as ambiguous in CHATEAU (/ʃato/) and non-ambiguous in MOTO (/moto/). And in BYCYCLETTE (/bisiklɛt/) the first /i/ was considered as non-ambiguous, and the second ambiguous. Criteria of frequency were those reported by Catach (1980); they concerned the general frequency of a particular PG mapping and not the frequency of a PG mapping in a particular sequential position, which is not available in French. One should point out that in French the most frequent PG mapping coincides with the most economically written transcription of a phoneme (thus /o/ is written O much more frequently than EAU or AU; /ɛ̃/ is written IN more frequently than EIN or AIN) with only few exceptions which appear in certain (infrequent) sequential positions (/k/ is written QU more frequently than K, /s/ is written SS more frequently than T). Orthographic ambiguity of French phonemes is summarized in Appendix 1.

TABLE 2. WRITING OF WORDS TO DICTATION. EFFECT OF DEGREE OF ORTHOGRAPHIC AMBIGUITY

Degree of orthographic ambiguity of a word	0	1	2 *and* 3
Examples	Madame /madam/	Mental /mɑ̃tal/	Anchois /ɑ̃ʃwa/ Gencive /ʒɑ̃siv/
No. of words	96	109	33
Percentage of correct responses	93	67	36

The patient wrote to dictation 238 words, whose orthographic degrees of ambiguity were variable (Table 2). The more orthographically ambiguous a word was the worse it was written; only 36 per cent of orthographically highly ambiguous words were written correctly. The transcription of these words was almost always phonetically correct (however ambiguous a word was, no more than 9 per cent of phonetic mistakes were observed). The errors stemmed almost exclusively from orthographic mistakes.

It was verified that the observed effect of orthographic ambiguity could not be reduced to the effects of length or frequency of the words. Length was evaluated by the number of phonemes forming the word (and not by the number of its letters, which is not totally independent of ambiguity and is therefore not relevant to a study of the effect of word length). Three classes of frequency (Juilland, Brodin and Davidovitch, 1970) were defined: F $<$ 1, 1 $\leqslant$ F $\leqslant$ 30 and F $\geqslant$ 31 per million. It is clear that length did not affect performance: the percentage (76 per cent) of correct responses for the 129 short words ($\leqslant$ 4 phonemes) was not statistically different from the percentage (70 per cent) of correct responses for the 109 long words ($\geqslant$ 5 phonemes) ($X_1^2 = 1.17$). Frequency significantly affected performance

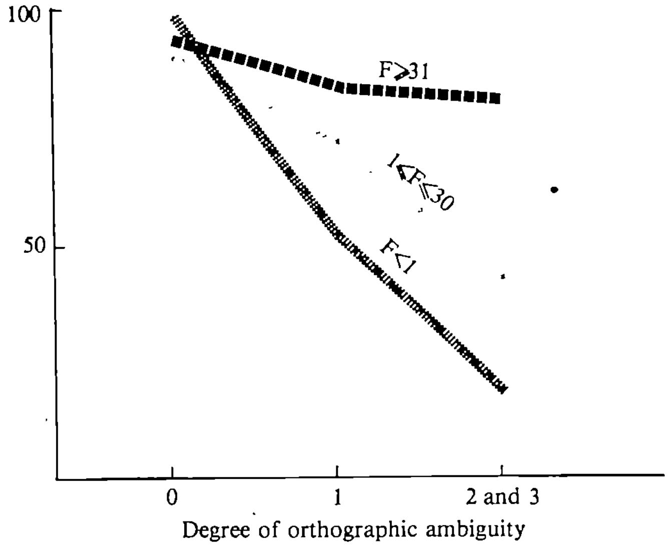

FIG. 1. Writing of words to dictation. Effect of degree of orthographic ambiguity and frequency of the words (percentages of correct responses). Degrees 2 and 3 have been grouped together because of the small number of words at degree 3.

$(X^2_2 = 13.67, P < 0.01)$. But fig. 1 shows that the effect of orthographic ambiguity could not be reduced to the effect of frequency, although there is an interaction between orthographic ambiguity and frequency.

In what way were the words incorrectly written? 64 out of 238 words were incorrectly written words and 77 errors were recorded because occasionally more than one error occurred in a word. All the errors for words consisted in writing non-words which nearly always had the same sound as the correct words. All the errors can be classified into one of the following classes (Table 3): omission or addition of a mute letter; changing one grapheme into another which has the same sound, either by changing one letter into another, or by changing one letter into two, or by changing two or three letters into one, or by changing the place of a mute letter; phonetic errors; and miscellaneous. The percentage of errors (18 per cent) which can be considered to be complication (addition of a mute letter and changing one letter into two) is much lower than the percentage of errors (48 per cent) which can be considered to be simplification (omission of a mute letter and changing two letters into one); however, the former type is not negligible.

It is noteworthy that a mute letter (Table 4) can be omitted or added, as well as sometimes correctly used; and, in the same way (Table 5) the graphemes corresponding to a given phoneme (for example, /o/ or /ɛ/) can be simplified, or complicated, as well as correctly used.

In the errors, the sequential transcription followed the rules of phoneme-grapheme conversion in French. For example, when a double consonant was used, it

TABLE 3. CLASSIFICATION OF THE ERRORS ON WORDS. SOME EXAMPLES

Omission of a mute letter	Habile→habil		
	Hochet→ochet		
	Orthographe→ortographe		25%
	Anchois→anchoi		
	Patient→patien		
	Coiffeur→coifeur		
Addition of a mute letter	Beauté→beautée		12%
	Comité→commité		
Changing a grapheme into another one which has the same phonetic value	Bicyclette→biciclette	y→i	
	Souk→souc	k→c	
	Tank→tanq	k→q	
	Gencive→gensive	c→s	
	Santal→cental	+ s→c an→en	17%
1 letter→another letter	Charpente→charpante	en→an	
	Serein→serain	ein→ain	
	Album→albom	um→om	
1 letter→2 letters	Photo→fauto	o→au	
	Église→aiglise	é→ai	6%
	Cavité→caviter	é→er	
2 or 3 letters→1 or 2 letter(s)	Fautif→fotif	au→o	
	Rameau→ramo	eau→o	
	Copeau→copot	eau→ot	
	Ainé→éner	ai→é	
	Meunier→menier	eu→e	
	Sœur→seur	œu→eu	23%
	Nain→nin	ain→in	
	S'agenouiller→s'agenouyer	ill→y	
	Magnétophone→magnétofone	ph→f	
	Équerre→ékerre	qu→k	
	Pigeon→pijon	ge→j	
Changing the place of one letter	Théâtre→téhatre		4%
Phonetic errors	Bœuf→feuf		
	Aveu→aveuf		9%
	Fauteuil→fauteui		
Miscellaneous	S'agenouiller→sa genouyer		4%

TABLE 4. EXAMPLES OF USING MUTE LETTERS

Grapheme under consideration	*Omission*	*Addition*	*Correct use*
Double letter	Coiffeur→coifeur	Comité→commité	Fourrure, vallée
Mute H	Hochet→ochet	Fauteuil→fhoteuil	Hôtel
Terminal mute letter	Habile→habil	Beauté→beautée	Armée, voiture

TABLE 5. EXAMPLES OF USING TWO-LETTER GRAPHEMES

Grapheme under consideration	*Simplification*	*Complexification*	*Correct use*
AI or E→/e/	Ainé→éner	Église→aiglise	Aidé
AU or O→/o/	Fautif→fotif	Photo→fauto	Jaunir

was always put between two vowels (for instance, COMMITÉ, BERRET) and never between a vowel and a consonant (there were no such errors as CHARRPENTE). A mute H was never placed in front of a consonant at the beginning of a word.

It was possible to compare the patient's writing to dictation of the same 20 words in 1975 and 1976. This permitted us to establish that the number of errors was comparable, and that the words which were correctly written were often the same (6 words out of 8 correct responses). But the errors themselves were most often different to the 14 errors made in 1975; only 6 were identical in 1976. For example: EQUERRE was written EQUERE and EKERRE; FAUTEUIL was written FAUTEUI and FOTEUIL; HABILE was written HABIL and ABILLE.

The following conclusions can be drawn from the error analysis as a whole: (a) It seems that the spelling errors were not due to systematic simplification of phoneme-grapheme conversion rules or to a failure of certain of these rules; (b) error-production seems to depend on certain characteristics of the word, since the errors appeared in the same word; given previous results, this can be simply explained in terms of variations in orthographic ambiguity of the word; (c) for this patient, there was no orthographic link between a word and its wrong spelling. It seems that, when confronted with the problem of writing words to dictation, he merely tried to use one of the possible (and normally the most economical) phoneme-grapheme conversion rules.

(3) *Writing irregular words to dictation* (*1979*). The test consisted of 52 orthographically irregular words (nouns and adjectives) of different frequency: 21 rare words (not listed in Juilland), 20 non-frequent words ($F \leqslant 30$) and 11 frequent words ($F \geqslant 31$). Only 38 per cent of the words were written correctly. There was a tendency for frequency of the words to affect performance but this was not statistically significant ($X_2^2 = 1.09$). It was observed that sometimes the patient seemed to remember that the word in question was irregular and then attempted to transcribe this irregularity, by using a number of conscious tricks. Some of them were unsuccessful; for instance, in the case of AUTOMNE, which is pronounced /ɔtɔn/, he wrote AUTOMME. Other ones were successful, as with use of a phonetic memory technique. For example, he wrote correctly TABAC, FUSIL, CROC, NERF, ESTOMAC—words where the last letter is irregularly mute—after saying each word with the mute letter pronounced and claiming it is spelled like that.

The patient's bad performance with orthographically ambiguous and irregular words is evidence of a severe impairment of the lexical writing process which produces spelling that is specific to a word. This impairment was not total since some of the orthographically irregular and highly ambiguous words were still correctly written and since frequency, that is a lexical variable, affected performance. On the other hand, it was impossible to discover in R.G. any sign of failure or simplification of certain phoneme-grapheme conversion rules. We can therefore admit that this patient showed a remarkable dissociation in writing between the normal operation of the phonological process and a severe impairment of the lexical process.

It might have been very interesting to test the ideas derived from the work of Glushko (1979), i.e., what matters is not whether the P.G. mapping is irregular, but whether there are other existing, inconsistent mappings. However, this work would have required special stimuli and our study was carried out before Glushko's paper was published.

II. Level of the Disturbance

(1) *The impairment was unrelated to the processing of auditorily presented words.* There were two kinds of evidence for this. First, auditorily presented words could be perfectly (or almost perfectly) repeated (Beauvois *et al.*, 1978), phonetically written and understood (the patient's IQ on the auditorily presented form of the Binois and Pichot's Synonym Test was 98). Secondly, the impairment was not restricted to auditory presentation of words (that is, writing words to dictation). It was also observed (with the same kind of errors) in spontaneous writing (Table 6) and in writing the names of 50 pictures of objects (Table 7).

TABLE 6. SPONTANEOUS WRITING (THE CORRECT SPELLING OF THE WORD IS ADDED IN BRACKETS)

Ile (il) m arive (arrive) que j'étouffe surtout le jour. Cette nuit j'ai bien dormi. J'ai été rassuré d'avoir une infirmiaire (infirmière) près de moi. J'avais tout ouver (ouvert), la grande porte et la fenaitre (fenêtre). La respiration va plus mal qu'ier (hier).

TABLE 7. ERRORS IN WRITING THE NAME OF 50 PICTURES OF OBJECTS

Balai	→	balais	Mètre	→	mettre
Thermomètre	→	termomètre	Bouilloire	→	bouyoir
Poèle	→	poèl	Lait	→	lai
Quille	→	bille	Escabeau	→	escabos
Béret	→	bérè	Arrosoir	→	arosoir
Entonnoir	→	entonoire	Épi	→	épie
Ceinture	→	cinture			

In standard examination, this task had not been especially designed to detect spelling errors and some of the target-words were homophonic to other ones. This is probably the reason why four of the errors (balais, mettre, lai, épie) were words that were homophonic to the target-words, whereas real words never occurred as errors in the dictation text, which was designed in such a way that no homophonic word could appear.

(2) *The impairment was not restricted to graphic output.* The spelling impairment was observed not only in writing, but also in two other tasks: pronouncing a word which began with a given spoken letter and spelling aloud a spoken word. When

asked to pronounce a word which began with a given spoken letter the patient sometimes (3/20) pronounced a word whose first sound corresponded to the sound of the proposed letter, but whose first letter did not correspond to it. Thus he said for E /oe/ → OEUF (/œf/), for I /i/ → HISTOIRE /istwaʀ/, for K /ka/ → CORRECT /kɔʀɛkt/.

The patient's performance in *spelling aloud a spoken stimulus* was comparable to his performance in writing to dictation. It had been observed (Beauvois and Dérouesné, 1979*a*) that the patient could perfectly spell out 40 non-words composed of 6 letters. By contrast when asked to spell out irregular or ambiguous words his performance was as much impaired as in writing to dictation, and the same kinds of error were recorded.

Tests of spelling aloud of words (1979) were designed to permit: (a) a comparison of performance on spelling aloud and on writing from dictation; (b) a systematic manipulation both of orthographic ambiguity and of other variables likely to affect the results: frequency, length and part-of-speech.

Spelling aloud 52 irregular words. The patient was asked to spell aloud the 52 irregular words that he had written to dictation a few days previously. The results were comparable to those registered for the dictation, although the level of performance was a little lower (only 21 per cent of the words were spelled correctly). There was a tendency for frequency of the words to affect performance but this was not statistically significant ($X^2_1 = 0.36$). Often the orthographic mistakes were different on dictation and in the spelling test (*see Appendix II*).

Spelling aloud 160 ambiguous nouns and adjectives. Three variables were manipulated: the degree of ambiguity of a word (0, 1, 2 and 3), its frequency ($\leqslant 30$ and $\geqslant 31$) and its length ($\leqslant 4$ phonemes and $\geqslant 5$ phonemes). In order to manipulate these three variables a factorial design including 16 experimental conditions was constructed. Each condition included about 10 words. The patient's

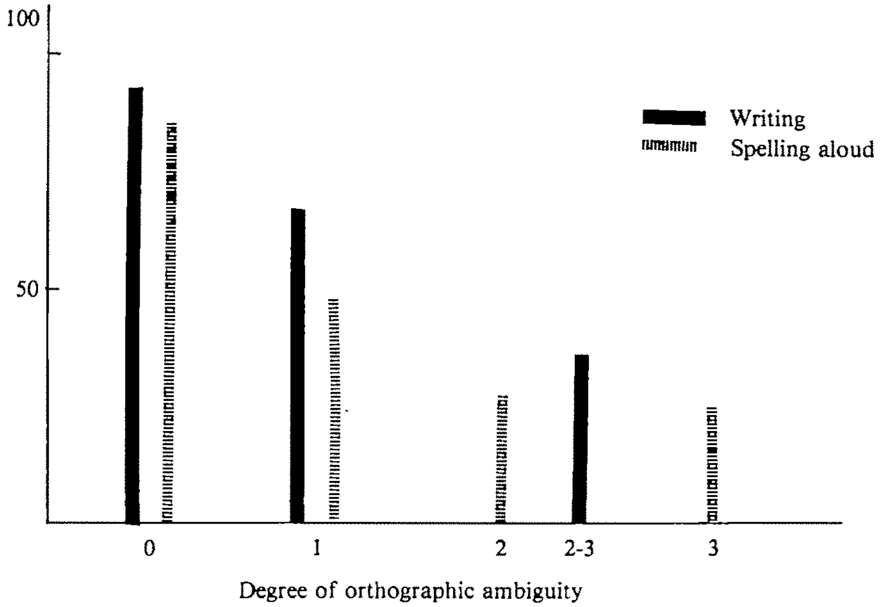

FIG. 2. Effect of degree of orthographic ambiguity in spelling aloud and writing to dictation.

performance on this task (fig. 2) was roughly comparable to his writing performance. The more orthographically ambiguous a word was, the worse it was spelled; length significantly affected performance ($X_1^2 = 9.06$, $P < 0.01$); as for writing there was an interaction between frequency and the degree of orthographic ambiguity (fig. 3).

Spelling aloud 119 grammatical words. Three variables were manipulated: the degree of ambiguity of a word (0, 1 and 2 and 3), its frequency ($\leqslant 30$ and $\geqslant 31$) and its meaningfulness, as we have previously defined it (Beauvois and Dérouesné, 1979*b*). As before, ambiguous words were significantly worse spelled than unambiguous words ($X_2^2 = 28.28$, $P < 0.01$; neither frequency ($X_1^2 = 0.03$), nor meaningfulness ($X_1^2 = 0.97$) affected performance significantly.

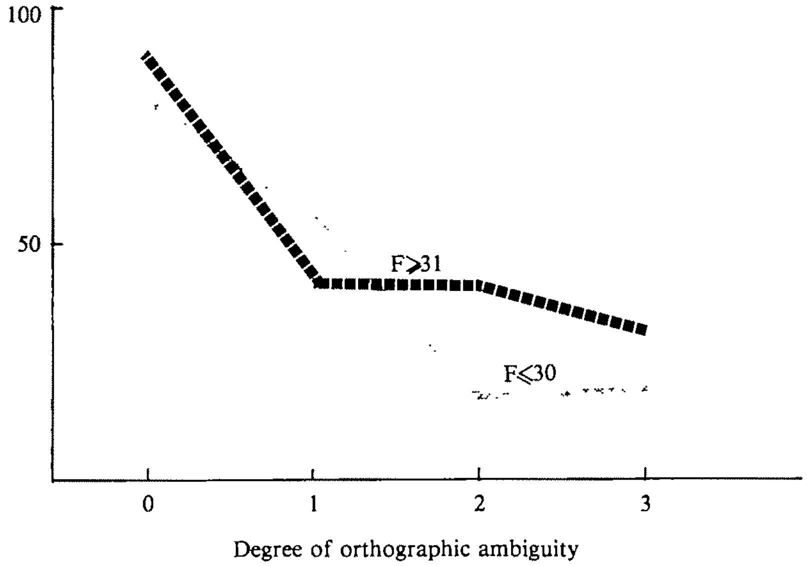

FIG. 3. Spelling aloud of 160 nouns and adjectives. Effect of degree of orthographic ambiguity and frequency of the words (percentages of correct responses).

Spelling aloud 20 inflected verbs. The patient was asked to spell aloud 20 inflected verbs, which were orally presented in a context that enabled him to identify the tense and the person of the verbs (for example, 'autrefois il *aidait* son père'). The verb-forms were chosen in such a way that the root and the inflexion were both ambiguous. Ten were frequent ($\geqslant 35$) and ten infrequent ($\leqslant 13$). The inflexions were as badly spelled (40 per cent of correct responses) as the roots (55 per cent of correct responses). Frequency did not significantly affect performance.

The findings of these tests may be summarized as follows: (1) the results obtained at two different times are comparable (since the results obtained in spelling aloud in 1979 are comparable with those obtained in writing to dictation in 1975–76); (2) the results obtained for spelling aloud and writing to dictation are roughly comparable (although they are slightly better in writing); (3) in spelling aloud part-of-speech did not significantly affect performance (fig. 4).

The disturbance observed in writing is therefore independent of an impairment of the processing of orally presented words; in particular if R.G. wrote words as non-words, it is not that he did not understand them, merely that he could not *spell* them; it is also independent of an impairment of graphic production. The disturbance involves the use of spelling independent of the understanding of a word and of graphic-writing.

III. Relationship Between Reading and Writing

A. *Reading versus writing: a double dissociation* (*1979*) (*fig. 5*). The patient was asked to read aloud the 52 orthographically irregular words that he had been asked to spell eight days previously: he was almost perfect at reading, whereas he had been very bad at spelling the words. Moreover, it has been seen (1) that the patient wrote non-words of 6 phonemes perfectly whereas it has been established (Beauvois and Dérouesné, 1979*a*) that he could only read 10 per cent of the non-words of 4 or 5 letters and of comparable syllabic complexity.

The disturbance observed in writing was therefore the reverse picture of the disturbance observed in reading: the patient used the lexical process in reading, whereas he used the phonological process in writing. This seems to mean that part at least of the lexical processing involved in reading is different from the lexical processing involved in writing; that is, the orthographic knowledge necessary for word-recognition in reading is different from the orthographic knowledge necessary for correct spelling in writing. If this is the case, the patient would be expected to be incapable of reading his own mis-spelling of the word he intended to write.

B. *Reading the mis-spelled words* (*1979*). The patient was asked to read the 190 orthographically irregular and ambiguous words that he had failed to spell aloud. These words were presented to him as he had spelled them. He failed to read his mis-spelling as the appropriate word in 45 per cent of these words; in this case, sometimes (38 per cent), he gave another word instead (for example, ALMANA (almanach) → 'album'; SOUVEN (souvent) → 'souvenir'; PLUSIEUR (plusieurs) → 'autour') but most often (62 per cent) he did not read anything and made remarks such as 'It's double-Dutch', 'It does not mean anything', 'It's not a word', 'Don't know it'. When he was able to read his mis-spelling as the appropriate word, he quite often (in 57 per cent of these words) made spontaneous remarks that demonstrated he knew the word was mis-spelled, for example, 'It's badly written, badly spelled', 'It's rather bizarre', 'Oh, what a mistake!'. Yet, when he tried to locate the mistake, either spontaneously or at the examiner's request, he failed with some rare exceptions. The stimuli that he was able to read differ by an average of 1.34 letters from the correct spelling, whereas the stimuli that he could not read differ by 1.92 from the correct word. The patient therefore seems to have been able to reconstitute a word from a non-word when there was not too great a difference between the two. Some of his remarks show clearly the way that he was guessing in the test. For instance, in the case of HALENE he said 'It could be haleine, but also Hélène'.

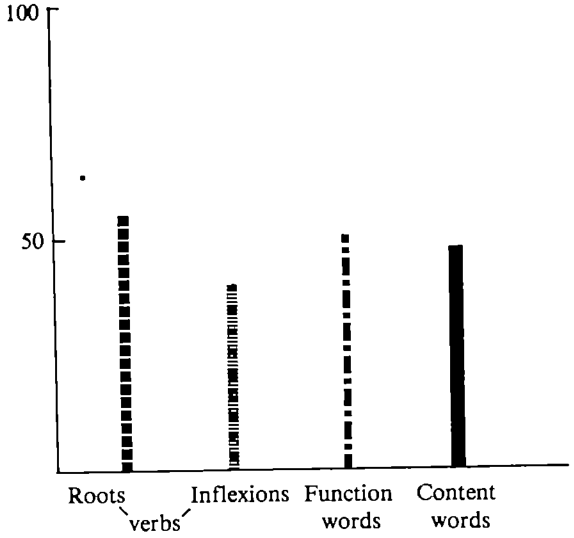

FIG. 4. Effect of part-of-speech variable on spelling aloud ambiguous words. Mean percentages of correct responses.

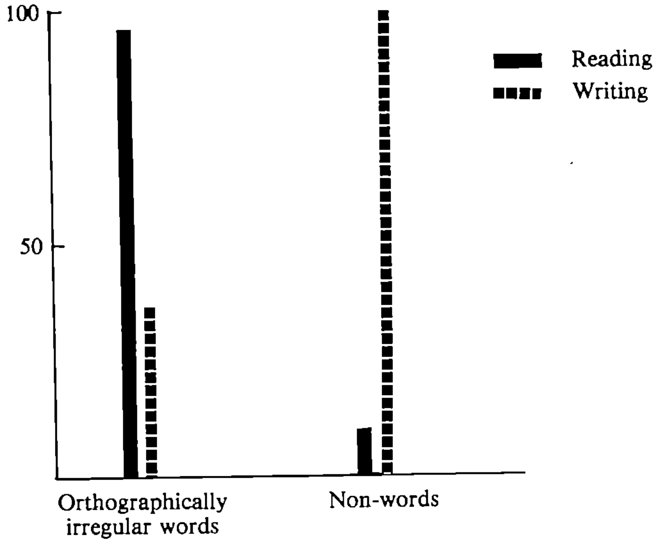

FIG. 5. Phonological writing and lexical reading (percentages of correct responses).

C. *Copying*. At first sight one result might seem to indicate the existence of an impairment of graphic output: when asked to copy from print to script the same 40 words that he had previously written to dictation, the patient made 4 errors which were similar to those recorded on dictation (for example, DIAMANT → DIAMENT; THEATRE → THEHATRE). This point will be discussed in the next section.

CONCLUSION

Three dissociations seem to be of particular interest with respect to the patient's writing: (a) in language production, the patient was suffering from an impairment of graphemic output, without comparable impairment of speech output; (b) in writing, he was suffering from an impairment of spelling without impairment of phoneme-grapheme conversion; (c) in visible language, he was suffering from an impairment of writing without equivalent impairment of reading. We will examine the implications of these dissociations for models of linguistic processes.

I. The patient's written word-production was impaired, whereas his oral word-production was unaffected. This dissociation corresponds to the dissociation usually observed in the rare but undeniable cases of pure agraphia, or, more generally, in all cases of agraphia without aphasia. But the point of interest here is that, as in some recent observations of this type (Dubois *et al.*, 1969; Assal *et al.*, 1970; Kinsbourne and Rosenfield, 1974), the agraphia was not linked to any motor or gestural impairment, but to an impairment of a linguistic process. This kind of dissociation constitutes the reverse picture of those cases in which there is impairment of oral production not due to an articulatory defect, without any impairment of written production (Lhermitte and Dérouesné, 1974; Michel, 1979). It is therefore further evidence to support the partial independence of the linguistic mechanisms used in the production of oral and written language. However, unlike the other reported cases in which the writing difficulty involved disturbances of phoneme-grapheme conversion either as one element (Hécaen *et al.*, 1963) or as the main element (Dubois *et al.*, 1969; Assal *et al.*, 1970; Kinsbourne and Rosenfield, 1974)—so resulting in phonemic paragraphia (for example, IRESTIABLE for IRRESISTIBLE, in Kinsbourne and Rosenfield)—in R.G. the spelling impairment was restricted to the particular spelling of a word, without affecting the sound-letter conversion.

II. In this patient's writing, phoneme-grapheme conversion was virtually unaffected, whereas spelling was much impaired. Such a contrast observed in writing between the perfect conservation of a phonological process (that is, writing by means of phoneme-grapheme conversion) and the severe impairment of a lexical process (that is, the production of the specific spelling of a word) recalls a somewhat similar dissociation between *Kanji* and *Kana* writing observed in a Japanese patient by Sasanuma and Monoi (1975). It has, however, as far as we know, never been reported in European patients. Hécaen *et al.* (1963) have indeed described a case of dysorthographia that corresponded to a severe impairment of lexical writing, but phonological writing was impaired as well, as indicated by the presence of numerous phonetic errors; in addition, the patient was not very literate. The important contrast observed in R.G. is equivalent to that already known in the reading of patients suffering from surface dyslexia (Marshall and Newcombe, 1973; Shallice and Warrington, 1980). It is, however, much purer to the extent that R.G. did not show any disturbance of phoneme-grapheme conversion, whereas the cases of surface dyslexia reported have shown defects of grapheme-phoneme conversion which have led to a questioning of the supposed dissociation between the two routes (Marcel, 1980). The purity of this dissociation leads us to postulate the existence of two independent writing processes, one phonological, the other non-phonological. The existence of a phonological agraphia (Shallice, 1981) characterized by complementary dissociation, constitutes supportive evidence for the existence of these two processes.

It therefore appears that all aspects of the patient's spelling can be explained in terms of one sole disturbance: namely, to a structure that permits the production of the spelling of words. Unfortunately, this does not fit the published data. It is, indeed, known that some patients cannot write words whereas they can spell them well enough (Dubois *et al.*, 1969) or even perfectly (Assal *et al.*, 1970; Kinsbourne and Rosenfield, 1974) without this being due to motor or gestural difficulties. And there are other patients who write better than they spell; according to Wapner and Gardner (1979), in almost all aphasics, writing is less impaired than spelling aloud, without this being necessarily related to an impairment of oral output. It is therefore likely that, if R.G.'s spelling impairment is seen to have the same characteristics in spelling-aloud and in writing, this is due to the presence of two different disturbances.

III. In R.G. the apparently complementary components are impaired in reading and in writing, respectively: phonological reading is impaired and lexical reading is intact; phonological writing is intact and lexical writing is impaired.

The association between an impairment of the phonological reading process and an impairment of the lexical writing process has also been found by Frith (1978, 1980) in children who spell badly whilst apparently reading well. If, as Frith argues, the spelling impairment results from a failure to acquire spellings related to the non-use of a phonological reading strategy (or, in her own terms, reading by full cues), it is clear that the reasons for the association of the two impairments are different. Of course, in the case of our patient, it might be asked whether his reading impairment did not affect his knowledge of spelling; that is, whether, when he lost the capacity to read words phonologically, this did not cause a progressive loss of the spelling of words. There is not evidence that this is the case. Indeed, the patient was examined for the first time one year after his operation, and the impairment was the same as four years later. It seems most implausible that spelling can be forgotten within a year, even if words are not read at all *via* grapheme-phoneme conversion during this period. Thus, in contrast to Frith's claims about her dyslexic children, the association in R.G. of a lexical writing impairment with a phonological reading impairment is probably fortuitous, and linked to the disturbance of two distinct functional systems. We can therefore examine separately the operation in reading and writing of the phonological processes and of the lexical processes.

R.G., who could read words and wrote them badly, showed an impairment of the lexical writing process without any impairment of the lexical reading process. This is evidence that orthographic knowledge involved in writing is different from orthographic knowledge involved in reading, or that word recognition processes in reading are totally different from word-production in writing, as assumed by Frith (1979) and by Morton (1980). Complementary evidence would be the observation of subjects who cannot read irregular words but who can spell them (surface dyslexia without lexical agraphia).

R.G., who could write non-words but could not read them, showed, therefore, an impairment of grapheme-phoneme conversion, without any impairment of phoneme-grapheme conversion (phonological alexia without phonological agraphia). Complementary evidence would be the observation of patients who cannot write non-words but who can read them (phonological agraphia without phonological alexia). If this is true, it constitutes evidence in favour of the independence of two phonological conversion processes used in writing and in reading: phoneme-grapheme conversion is independent of grapheme-phoneme conversion. Consequently this also constitutes evidence against certain models (Weigl and Fradis, 1977; Dubois, 1977) which assume that writing from dictation involves transcoding from the phonetic level to the visual graphemic level, with this graphemic level identical to that involved in reading. More generally, this indicates that in any patient suffering from alexia with agraphia at least two disturbances must be assumed.

A final result involving the relationship between reading and writing requires comment: when asked to copy words from *print* to *script*, the patient made errors that were similar to those recorded in dictation. Obviously, this copying impairment does not necessarily point, as has often been thought, to a visual or gestural impairment. In our opinion, this was a consequence of the patient's writing and reading impairments operating together. There are at least two possible strategies for copying from print to script, and both of them were disturbed in this patient. The first is to transcribe stimuli by means of grapheme-phoneme plus phoneme-grapheme conversion; because of his phonological alexia, this patient could not carry out the grapheme-phoneme conversion, this resulting in particular in poor copying of non-words (22 per cent correct responses) (Beauvois and Dérouesné, 1979*a*). The second strategy is to use the semantic or lexical route, with words, and this is how he proceeded, but because of his orthographic disturbance he was not completely successful. Like dictation (Ammon, 1979) copy-writing can, therefore, sometimes be a very sensitive test for detecting high level disturbances of the linguistic processes.

SUMMARY

A case of agraphia was studied in the framework of the information-processing approach and in relation to comparable studies on alexia. Three dissociations are of interest in this patient's picture: (a) in language production: impairment of writing without impairment of speech; (b) in writing: impairment of spelling without impairment of phoneme-grapheme conversion; (c) in visible language: impairment of writing without equivalent impairment of reading. The implications of these dissociations for any model of linguistic processes are discussed.

ACKNOWLEDGEMENTS

We wish to thank N. Catach who provided us with personal data on French orthography. We are grateful to Danièle Marinolli, who assisted us in building some of the tests. We thank J. L. Beauvois, C. Dérouesné, J. L. Signoret and G. Deloche for comments on an early draft. We thank J. K. Hylton for help in translation.

The study was supported by a grant of Conseil Scientifique de la Faculté de Médecine Pitié-Salpêtrière, Université de Paris VI.

APPENDIX I. ORTHOGRAPHIC AMBIGUITY OF FRENCH PHONEME-GRAPHEME MAPPINGS

Frequency of PG mappings comes from Catach (1974, 1980, and personal communication).

What is considered is the phoneme and not its possible different phonetic forms.

Accents have not been taken into account.

U = Unambiguous. A = Ambiguous. PG = The choice between possible transcriptions is determined by phoneme-grapheme sequential conversion rules, and not by lexical orthographic knowledge.

1. PHONEMES WHICH ARE ALWAYS UNAMBIGUOUS

Phonemes	*Graphemes*	*Frequency* %	*Ambiguity*	*Phonemes*	*Graphemes*	*Frequency* %	*Ambiguity*
/a/ or /ɑ/	A	100	U	/d/	D	100	U
/y/	U	100	U	/g/	G GU	100	U U } PG
/u/	OU	100	U	/v/	V	100	U
/ɔ̃/	ON OM	92.8	U U } PG	/ʃ/	CH	100	U
/œ̃/	UN	97	U	/l/	L	100	U
/wa/	OI	100	U	/ʀ/	R	100	U
/wɛ̃/	OIN	100	U	/m/	M	100	U
/p/	P	100	U	/n/	N	100	U
/b/	B	100	U	/ɲ/	GN	100	U
/t/	T	99	U				

2. Phonemes which Can be Ambiguous

Phonemes	*Graphemes*	*Frequency* %	*Ambiguity*
/i/	I	98	U
	Y	2	A
/e/	E or É	99	U (PG)
	AI		A
/ɛ/	E or È	67.9	U (PG)
	AI	30	A
/ø/, /œ/ and /ə/	E	(most frequent)	U
	EU		U or A (PG)
	ŒU		A
/o/ and /ɔ/	O	75	U
	AU	21	A
	EAU	3	A
/ɛ̃/	IN	45	U
	EN	23	U (PG)
	AIN		A
	AIM		A
	EIN		A
/ɑ̃/	AN	44	A
	EN	47	A
	EM		A
	AM		A
/j/	I	86	U
	ILL	10	U or A (PG)
	Y	3	U or A (PG)
/f/	F	95	U
	PH		A
/z/	S	90	U
	Z	10	U or A (PG)
/ʒ/	J	49	U or A (PG)
	G or GE	51	A (PG)
/s/	S	54	U
	C	27	U or A (PG)
	SS	12	U or A (PG)
	T	4	A
	Ç	1	A
/k/	C	57.8	U
	QU	42.2	U or A (PG)
	K	< 1	A

APPENDIX II. STIMULUS WORDS AND SUBJECT'S RESPONSES IN WRITING AND SPELLING ALOUD

DOA = degree of orthographic ambiguity. F = frequency per million. L = long word ($\geqslant 5$ phonemes). S = short word ($\leqslant 4$ phonemes).

1. Writing 238 Words having Various DOA (1976; Post Hoc *Analysis)*

Target word	*Phonetic transcription*	*Patient's response*	*Target word*	*Phonetic transcription*	*Patient's response*
DOA = 0; F < 1; S					
bouquin	/bukɛ̃/	+	filou	/filu/	+
moto	/mɔtɔ/	+	soda	/sɔda/	+
dodu	/dɔdy/	+	visa	/viza/	+
défi	/defi/	+	veuf	/vœf/	+
pari	/paʀi/	+	oursin	/uʀsɛ̃/	+
roti	/ʀoti/	+	bouquin	/bukɛ̃/	+
bouc	/buk/	+			
DOA = 0; 1 ⩽ F ⩽ 30; S					
canon	/kanɔ̃/	+	poli	/pɔli/	+
vêtu	/vety/	+	menu	/məny/	+
café	/kafe/	+	four	/fuʀ/	+
doré	/dɔʀe/	+	bonté	/bɔ̃te/	+
curé	/kyʀe/	+	aveu	/avø/	aveuf
ravi	/ʀavi/	+	lundi	/lœ̃di/	+
unir	/yniʀ/	iunir			

Target word	*Phonetic transcription*	*Patient's response*	*Target word*	*Phonetic transcription*	*Patient's response*
DOA = 0; F ⩾ 31; S					
avion	/avjɔ̃/	+	joli	/ʒɔli/	+
cour	/kuʀ/	+	leur	/lœʀ/	lheur
cheveu	/ʃəvø/	+	peur	/pœʀ/	+
neuf	/nœf/	+	jour	/ʒuʀ/	+
odeur	/ɔdœʀ/	+	avion	/avjɔ̃/	+
tour	/tuʀ/	+	cheveu	/ʃəvø/	+
pour	/puʀ/	+	papa	/papa/	+
papa	/papa/	+	seul	/sœl/	+
mari	/maʀi/	+			
DOA = 0; F ⩽ 1; L					
cascade	/kaskad/	+	cavité	/kavite/	caviter
bocal	/bɔkal/	+	labour	/labuʀ/	+
canif	/kanif/	+	abusif	/abyzif/	+
amical	/amikal/	+	sureté	/syʀ(ə)te/	+
mécano	/mekano/	+	rêveur	/ʀɛvœʀ/	+
canari	/kanaʀi/	+	saveur	/savœʀ/	+
périmé	/peʀime/	+	averse	(avɛʀs(ə)/	+
démoli	/demɔli/	+			
DOA = 0; 1 ⩽ F ⩽ 30; L					
métro	/metʀɔ/	+	moteur	/mɔtœʀ/	+
péril	/peʀil/	périf	cuisine	/kyizin/	+
débuté	/debyte/	+	samedi	/sam(ə)di/	+
séjour	/seʒuʀ/	+	désolé	/dezɔle/	+
poisson	/pwasɔ̃/	+	voleur	/vɔlœʀ/	+
revenu	/ʀ(ə)vəny/	+	soupir	/supiʀ/	+
décoré	/dekɔʀe/	+	métro	/metʀɔ/	+
retenu	/ʀət(ə)ny/	+	moteur	/mɔtœʀ/	+
défilé	/defile/	+	cuisine	/kyizin/	+
numéro	/nymeʀo/	+	moteur	/mɔtœʀ/	+
comité	/kɔmite/	commité	poisson	/pwasɔ̃/	+
détour	/detuʀ/	+			
DOA = 0; F ⩾ 31; L					
cheval	/ʃ(ə)val/	+	docteur	/dɔktœʀ/	+
fenêtre	/f(ə)nɛtʀ(ə)/	+	amusé	/amyze/	+
montagne	/mɔ̂taɲ/	+	jardin	/ʒaʀdɛ̃/	+
ramené	/ʀam(ə)ne/	+	mourir	/muʀiʀ/	+
retour	/ʀ(ə)tuʀ/	+	madame	/madam/	+
prison	/pʀizɔ̃/	+	madame	/madam/	+
église	/egliz/	aiglise			
DOA = 1; F < 1; S					
béret	/beʀɛ/	berret	forain	/fɔʀɛ̃/	+
ilôt	/ilo/	ilo	rateau	/ʀɑto/	+
ourlet	/uʀlɛ/	+	rameau	/ʀamo/	ramo
copeau	/kɔpo/	+	radeau	/ʀado/	radedeau
ainé	/ene/	èner	levain	/ləvɛ̃/	+
daim	/dɛ̃/	+	souk	/suk/	souc
tain	/tɛ̃/	+	béret	/beʀɛ/	+
nain	/nɛ̃/	nin	copeau	/kɔpo/	copot
étain	/etɛ̃/	+	équerre	/ekɛʀ/	ékerre
seau	/so/	+	équerre	/ekɛʀ/	équere
serein	/səʀɛ̃/	serain			

Target word	*Phonetic transcription*	*Patient's response*	*Target word*	*Phonetic transcription*	*Patient's response*
DOA = 1; 1 ⩽ F ⩽ 30; S					
graine	/gʀɛn/	+	boeuf	/bœf/	feuf
pigeon	/piʒɔ̃/	+	rideau	/ʀido/	ridot
herbe	/ɛʀb(ə)/	erbe	dédain	/dedɛ̃/	+
genou	/ʒ(ə)nu/	+	gateau	/gɑto/	+
repas	/ʀ(ə)pɑ/	+	cadeau	/kado/	+
ballon	/balɔ̃/	+	coteau	/kɔto/	coto
pair	/pɛʀ/	+	caveau	/kavo/	+
élan	/elɑ̃/	+	vilain	/vilɛ̃/	+
oeuf	/œf/	+	sain	/sɛ̃/	+
veau	/vo/	+	sein	/sɛ̃/	+
gain	/gɛ̃/	+	graine	/gʀɛn/	+
rein	/ʀɛ̃/	rain	pigeon	/piʒɔ̃/	pijon
vain	/vɛ̃/	+	herbe	/ɛʀb(ə)/	erbe
faim	/fɛ̃/	+	genou	/ʒ(ə)nu/	+
bain	/bɛ̃/	+	repas	/ʀ(ə)pɑ/	+
voeu	/vø/	veu	ballon	/balɔ̃/	+
DOA = 1; F ⩾31; S					
photo	/fɔto/	fauto	hôtel	/otɛl/	+
chateau	/ʃɑto/	+	beau	/bo/	+
aidé	/ede/	+	demain	/d(ə)mɛ̃/	+
pain	/pɛ̃/	+	maison	/mɛzɔ̃/	+
peau	/po/	+	main	/mɛ̃/	+
bateau	/bato/	+	photo	/fɔto/	+
beauté	/bote/	beáutée	chateau	/ʃɑto/	+
oiseau	/wazo/	+	peine	/pɛn/	+
soeur	/sœʀ/	seur	maison	/mɛzɔ̃/	+
peine	/pɛn/	+	ainsi	/ɛ̃si/	+
armée	/aʀme/	+			
DOA = 1; F < 1; L					
potion	/posjɔ̃/	+	fautif	/fotif/	fotif
album (irreg.)	/albɔm/	+	mental	/mɑ̃tal/	+
magnétophone	/maɲetɔfɔn/	magnétaubonne	empiler	/ɑ̃pile/	empiller
levure	/l(ə)vyʀ/	+	épaulé	/epole/	+
volcan	/vɔlkɑ̃/	+	charpente	/ʃaʀpɑ̃t/	charpante
rature	/ʀatyʀ/	+	coiffeur	/kwafœʀ/	coifeur
voilier	/vwalje/	+	santal	/sɑ̃tal/	cental
essuyer	/ɛsɥije/	+	jaunir	/ʒoniʀ/	+
essuyer	/ɛsɥije/	+	album (irreg.)	/albɔm/	albom
bretelle	/bʀətɛl/	+	magnétophone	/maɲetɔfɔn/	magnétofone
rivage	/ʀivaʒ/	+	coiffeur	/kwafœʀ/	coiffeure
DOA = 1; 1 ⩽ F ⩽ 30; L					
drapeau	/dʀapo/	+	fauteuil	/fotœj/	fhoteuil
bouteille	/butɛj/	+	fauteuil	/fotœj/	fauteui
étendu	/etɑ̃dy/	+	ressort	/ʀ(ə)sɔʀ/	ressor
DOA = 1; F ⩾ 31; L					
papier	/papje/	+	papier	/papje/	+
voiture	/vwatyʀ/	+	voiture	/vwatyʀ/	+
théâtre	/teɑtʀ(ə)/	téhatre	théâtre	/teɑtʀ(ə)/	téhatre
tableau	/tablo/	+	sentir	/sɑ̃tiʀ/	+
poussière	/pusjɛʀ/	+			
DOA = 2; F < 1; S					
anchois	/ɑ̃ʃwa/	anchoi	tank	/tɑ̃k/	tanq

Target word	*Phonetic transcription*	*Patient's response*	*Target word*	*Phonetic transcription*	*Patient's response*
DOA = 2; 1 ⩽ F ⩽ 30; S					
habile	/abil/	habil	ranger	/ʀɑ̃ʒe/	+
hangar	/ɑ̃gaʀ/	engare	habile	/abil/	abille
hochet	/ɔʃɛ/	ochet	ranger	/ʀɑ̃ʒe/	+
vallée	/vale/	+			
DOA = 2; F < 1; L					
bicyclette	/bisiklɛt/	biciclete	orthographe	/ɔʀtɔgʀaf/	ortografe
encrier	/ɑ̃kʀije/	+	bicyclette	/bisiklɛt/	byciclette
orthographe	/ɔʀtɔgʀaf/	ortographe	chaussure	/ʃosyʀ/	+
meunier	/mønje/	menier	s'agenouiller	/saʒ(ə)nuje/	sa genouyer
encrier	/ɑ̃kʀije/	+	s'agenouiller	/saʒ(ə)nuje/	sa genouyer
DOA = 2; 1 ⩽ F ⩽ 30; L					
prairie	/pʀeʀi/	+	s'habiller	/sabije/	sabiller
diamant	/djamɑ̃/	diament	s'habiller	/sabije/	s'abiller
fourrure	/fuʀyʀ/	+			
DOA = 2; F ⩾ 31; L					
village	/vilaʒ/	vilage			
village	/vilaʒ/	+			
DOA = 3; F < 1; L					
patient	/pasjɑ̃/	patien	gencive	/ʒɑ̃siv/	gensive
gencive	/ʒɑ̃siv/	gensive	patient	/pasjɑ̃/	patien
DOA = 3; F ⩾ 31; S					
gentil (irreg.)	/ʒɑ̃ti/	+			
gentil (irreg.)	/ʒɑ̃ti/	+			
enfant	/ɑ̃fɑ̃/	+			

2. *Spelling Aloud of 160 Ambiguous Nouns and Adjectives* (*1979; Experimentally Designed*)

Target word	*Phonetic transcription*	*Patient's response*	*Target word*	*Phonetic transcription*	*Patient's response*
DOA = 0; F ⩽ 30; S					
arbre	/aʀbʀ(ə)/	+	lundi	/lœ̃di/	+
choc	/ʃɔk/	+	pape	/pap/	+
curé	/kyʀe/	+	tissu	/tisy/	+
four	/fuʀ/	+	trou	/tʀu/	+
lien	/ljɛ̃/	+	bourse	/buʀs(ə)/	+
DOA = 0; F ⩾ 31; S					
carte	/kaʀt(ə)/	+	ligne	/liɲ/	+
chemin	/ʃ(ə)mɛ̃/	+	mode	/mɔd/	+
coin	/kwɛ̃/	+	papa	/papa/	+
dame	/dam/	+	terme	/tɛʀm(ə)/	+ (therme)
étude	/etyd/	éthude	tour	/tuʀ/	+
DOA = 0; F ⩽ 30; L					
bûcheron	/byʃ(ə)ʀɔ̃/	+	ingratitude	/ɛ̃gʀatityd/	ingratitume
charité	/ʃaʀite/	+	moustache	/mustaʃ/	moustace
touriste	/tuʀist(ə)/	+	numéro	/nymeʀo/	+
détour	/detuʀ/	+	obscurité	/ɔpskyʀite/	obsquirité
district	/distʀik(t)/	distrique	tribunal	/tʀibynal/	+

Target word	*Phonetic transcription*	*Patient's response*	*Target word*	*Phonetic transcription*	*Patient's response*
$DOA = 0; F \geqslant 31; L$					
pardon	/paʀdɔ̃/	+	montagne	/mɔ̃taɲ/	+
espoir	/ɛspwaʀ/	+	problème	/pʀɔblɛm/	+
fenêtre	/f(ə)nɛtʀ(ə)/	+	retour	/ʀ(ə)tuʀ/	+
liberté	/libɛʀte/	+	spectacle	/spɛktakl(ə)/	spetagle
ministre	/ministʀ(ə)/	+	vérité	/veʀite/	+
$DOA = 1; F \leqslant 30; S$					
chameau	/ʃamo/	+	genou	/ʒ(ə)nu/	+
drap	/dʀa/	+	herbe	/ɛʀb(ə)/	erbe
éloge	/elɔʒ/	+	dégoût	/degu/	degou
évêque	/evɛk/	+	leçon	/l(ə)sɔ̃/	+
flot	/flo/	+	juillet	/ʒɥijɛ/	+
galop	/galo/	galo			
$DOA = 1; F \geqslant 31; S$					
pierre	/pjɛʀ/	+	goût	/gu/	+
début	/deby/	débu	honte	/ɔ̃t/	onte
école	/ekɔl/	+	hôtel	/otɛl/	+
éclat	/ekla/	écla	maman	/mamɑ̃/	+
château	/ʃɑto/	+	pays	/pei/	paihi
$DOA = 1; F \leqslant 30; L$					
bistrot	/bistʀo/	bistro	écrivain	/ekʀivɛ̃/	+
boulevard	/bul(ə)vaʀ/	boulevart	fourneau	/fuʀno/	+
catastrophe	/katastʀɔf/	catastrofe	habileté	/abil(ə)te/	+
chapelle	/ʃapɛl/	chapele	crépuscule	/kʀepyskyl/	crépuscul
discussion	/diskysjɔ̃/	discution			
$DOA = 1; F \geqslant 31; L$					
atmosphère	/atmɔsfɛʀ/	atmosefer	sommeil	/sɔmɛj/	sommei
garçon	/gaʀsɔ̃/	garcon	origine	/ɔʀiʒin/	orijine
habitude	/abityd/	abitude	industrie	/ɛ̃dystʀi/	hindustri
méthode	/metɔd/	métode	résultat	/ʀezylta/	resulta
principe	/pʀɛ̃sip/	+	système	/sistɛm/	sistème
république	/ʀepyblik/	+	semaine	/s(ə)mɛn/	+
$DOA = 2; F \leqslant 30; S$					
anneau	/ano/	anno	héros	/ɛʀo/	éro
bonnet	/bɔnɛ/	bonnai	lycée	/lise/	lissé (un)
ange	/ɑ̃ʒ/	+	manteau	/mɑ̃to/	manto
étang	/etɑ̃/	étant (un)	rançon	/ʀɑ̃sɔ̃/	ranson
habit	/abi/	habi	banquet	/bɑ̃kɛ/	+
haleine	/alɛn/	halene			
$DOA = 2; F \geqslant 31; S$					
accord	/akɔʀ/	+	effort	/efɔʀ/	+
année	/ane/	anné	neige	/nɛʒ/	neje
défaut	/defo/	desfaut	paix	/pɛ/	pai
génie	/ʒeni/	geni	terrain	/tɛʀɛ̃/	+
hasard	/azaʀ/	hazare	style	/stil/	+
sujet	/syʒɛ/	+			

Target word	Phonetic transcription	Patient's response	Target word	Phonetic transcription	Patient's response
DOA = 2; F ⩽ 30; L					
silhouette	/silwɛt/	silouete	bourgeoisie	/buʀʒwazi/	bourjoisi
faubourg	/fobuʀ/	fauboure	magistrat	/maʒistʀa/	magistra
appétit	/apeti/	appèti	enthousiasme	/ɑ̃tuzjasm(ə)/	entousiasme
photographe	/fɔtɔgʀaf/	photografe	ascension	/asɑ̃sjɔ̃/	acention
héritage	/eʀitaʒ/	+	syndicat	/sɛ̃dika/	syndica
scandale	/skɑ̃dal/	+	habitation	/abitasjɔ̃/	abitation
dactylographe	/daktilɔgʀaf/	dactilográfe			
DOA = 2; F ⩾ 31; L					
immensité	/im(m)ɑ̃site/	imencité	rapport	/ʀapɔʀ/	rappor
histoire	/istwaʀ/	hystoire	village	/vilaʒ/	+
énergie	/enɛʀʒi/	enerji	commission	/kɔmisjɔ̃/	comision
lendemain	/lɑ̃d(ə)mɛ̃/	lendemin	immensité	/im(m)ɑ̃site/	+
littérature	/liteʀatyʀ/	literature	janvier	/ʒɑ̃vje/	+
quantité	/kɑ̃tite/	+			
DOA = 3; F ⩽ 30; S					
ciment	/simɑ̃/	+	hommage	/ɔmaʒ/	+
agent	/aʒɑ̃/	agen	monnaie	/mɔnɛ/	monais
attrait	/atʀɛ/	attrai	torrent	/tɔʀɑ̃/	torran
faisceau	/fɛso/	faissau	vaisseau	/vɛso/	vaisso
DOA = 3; F ⩾ 31; S					
argent	/aʀʒɑ̃/	argen	enfant	/ɑ̃fɑ̃/	+
danger	/dɑ̃ʒe/	+	horaire	/ɔʀɛʀ/	+
argent	/aʀʒɑ̃/	+	danger	/dɑ̃ʒe/	+
enfant	/ɑ̃fɑ̃/	enfan	horaire	/ɔʀɛʀ/	aurraire
gens	/ʒɑ̃/	jens			
DOA = 3; F ⩽ 30; L					
gymnastique	/ʒimnastik/	gimnastique	rendez-vous	/ʀɑ̃devu/	rendévou
éléphant	/elefɑ̃/	élephan	sangfroid	/sɑ̃fʀwa/	sanfroi
hypocrisie	/ipɔkʀizi/	hipogrisi	hypothèse	/ipɔtɛz/	hypotèse
cyprès	/sipʀɛ/	cipré	augmentation	/ɔgmɑ̃tɑsjɔ̃/	+
DOA = 3; F ⩾ 31; L					
philosophie	/filɔzɔfi/	fylosofi	jeunesse	/ʒœnɛs/	jenesse
développement	/dev(ə)lɔp(ə)mɑ̃/	dévelopement	printemps	/pʀɛ̃tɑ̃/	printemp
printemps	/pʀɛ̃tɑ̃/	printent	jeunesse	/ʒœnɛs/	jenesse
philosophie	/filɔzɔfi/	philosofi			

3. *Spelling Aloud of 119 Function Words* (*1979*)

Target word	Phonetic transcription	Patient's response
DOA = 0; F ⩽ 30; meaningless		
duquel	/dykɛl/	+
duquel	/dykɛl/	+
duquel	/dykɛl/	+

Target word	*Phonetic transcription*	*Patient's response*	*Target word*	*Phonetic transcription*	*Patient's response*
DOA = 0; F ⩾ 31; meaningless					
te	/tə/	+	voilà	/vwala/	+
donc	/dɔ̃k/	+	malgré	/malgʀe/	+
votre	/vɔtʀ(ə)/	vautre	sinon	/sinɔ̃/	sinont
notre	/nɔtʀ(ə)/	+	selon	/s(ə)lɔ̃/	+
combien	/kɔ̃bjɛ̃/	+	quel	/kɛl/	+
parmi	/paʀmi/	+	lequel	/ləkɛl/	+
voici	/vwasi/	voissi			
DOA = 0; F ⩽ 30; meaningful					
mien	/mjɛ̃/	+	sien	/sjɛ̃/	+
mien	/mjɛ̃/	+	sien	/sjɛ̃/	+
DOA = 0; F ⩾ 31; meaningful					
oui	/wi/	+	chacun	/ʃakœ̃/	chaqun
vite	/vit/	+	déjà	/deʒa/	+
ici	/isi/	+	chacune	/ʃakyn/	+
toute	/tut/	+	jadis	/ʒadis/	+
DOA = 1; F ⩽ 30; meaningless					
sitôt	/sito/	+	environ	/ɑ̃viʀɔ̃/	+
environ	/ɑ̃viʀɔ̃/	+	sitôt	/sito/	sito
environ	/ɑ̃viʀɔ̃/	+			
DOA = 1; F ⩾ 31; meaningless					
ainsi	/ɛ̃si/	+	celui	/səlɥi/	+
nos	/no/	neau	toutefois	/tut(ə)fwa/	toutefoi
comme	/kɔm/	+	laquelle	/lakɛl/	+
chaque	/ʃak/	+	laquelle	/lakɛl/	laqelle
ceci	/səsi/	cessi	jusque	/ʒysk(ə)/	+
autour	/otuʀ/	+	puisque	/pɥisk(ə)/	+
alors	/alɔʀ/	+	lorsque	/lɔʀsk(ə)/	+
plutôt	/plyto/	+	quelque	/kɛlk(ə)/	+
ainsi	/ɛ̃si/	ainci	quelque	/kɛlk(ə)/	+
DOA = 1; F ⩽ 30; meaningful					
tienne	/tjɛn/	+	mienne	/mjɛn/	miene
mienne	/mjɛn/	miène	debout	/dəbu/	+
debout	/dəbu/	debou	autrui	/otʀɥi/	+
autrui	/otʀɥi/	+	alentour	/alɑ̃tuʀ/	allentour
alentour	/alɑ̃tuʀ/	allentour	quiconque	/kikɔ̃k/	+
tienne	/tjɛn/	+			
DOA = 1; F ⩾ 31; meaningful					
chez	/ʃe/	ché	parfois	/paʀfwa/	parfoi
enfin	/ɑ̃fɛ̃/	+	pourquoi	/puʀkwa/	+
autre	/otʀ(ə)/	hotre	depuis	/dəpɥi/	depui
demain	/d(ə)mɛ̃/	+	plusieurs	/plyzjœʀ/	plusieur
bientôt	/bjɛ̃to/	biento	depuis	/dəpɥi/	+
partout	/paʀtu/	partou	plusieurs	/plyzjœʀ/	plusieur
ensuite	/ɑ̃sɥit/	+	quelquefois	/kɛlkəfwa/	queltefoi
surtout	/syʀtu/	+	ailleurs	/ajœr/	ailleur
toujours	/tuʒuʀ/	toujour			

Target word	Phonetic transcription	Patient's response	Target word	Phonetic transcription	Patient's response
DOA = 2 or 3; F ⩽ 30; meaningless					
hormis	/ɔʀmi/	ormi	hormis	/ɔʀmi/	ormi
quoique	/kwak(ə)/	+	quoique	/kwak(ə)/	+
desquels	/dekɛl/	dequels	desquels	/dekɛl/	desquel
néanmoins	/neɑ̃mwɛ̃/	neanmoi	néanmoins	/neɑ̃mwɛ̃/	néanmoin
moyennant	/mwajɛnɑ̃/	moyainan	moyennant	/nwajɛnɑ̃/	moi
auparavant	/opaʀavɑ̃/	auparavan	auparavant	/opaʀavɑ̃/	au paravant
dorénavant	/dɔʀenavɑ̃/	dorénavent	dorénavant	/dɔʀenavɑ̃/	dorénavent
DOA = 2 or 3; F ⩾ 31; meaningless					
aussi	/osi/	ossi	aussi	/osi/	+
tantôt	/tɑ̃to/	tanto	tantôt	/tɑ̃to/	tanto
certes	/sɛʀt(ə)/	certe	certes	/sɛʀt(ə)/	certe
pourtant	/puʀtɑ̃/	+	pourtant	/puʀtɑ̃/	+
lesquels	/lekɛl/	lesquel	lesquels	/lekɛl/	lesquel
DOA = 2 or 3; F ⩽ 30; meaningful					
volontiers	/vɔlɔ̃tje/	volontier			
DOA = 2 or 3; F ⩾ 31; meaningful					
auprès	/opʀɛ/	+	comment	/kɔmɑ̃/	+
souvent	/suvɑ̃/	souven	aussitôt	/osito/	ossiteau
beaucoup	/boku/	boquou	aujourd'hui	/oʒuʀdɥi/	aujourdui
jamais	/ʒamɛ/	jamai	auprès	/opʀɛ/	aupré
encore	/ɑ̃kɔʀ/	enquor	souvent	/suvɑ̃/	+
désormais	/dezɔʀmɛ/	desormai	aujourd'hui	/oʒuʀdɥi/	aujourdui
davantage	/davɑ̃taʒ/	daventage	assez	/ase/	aset
autant	/otɑ̃/	autan			

4. Spelling Aloud of 20 Verbs (*1979*)

Target word	Phonetic transcription	Patient's response	Target word	Phonetic transcription	Patient's response
(*35 < F < 553*)					
aimaient	/emɛ/	+	mangeaient	/mɑ̃ʒɛ/	mengais
causèrent	/kozɛʀ/	cauzèrent	nommerait	/nɔm(ə)ʀɛ/	nomerai
cessent	/sɛs/	saisent	abandonnèrent	/abɑ̃dɔnɛʀ/	abandonnere
entrerais	/ɑ̃tʀəʀɛ/	entrer	commençait	/kɔmɑ̃sɛʀ/	commençai
aidait	/edɛ/	eddai	taisent	/tɛz/	+
(*7 < F < 13*)					
logeaient	/lɔʒɛ/	logaient	erraient	/ɛʀɛ/	+
dansèrent	/dɑ̃sɛʀ/	danssèrent	vengeait	/vɑ̃ʒɛ/	vengé
lançait	/lɑ̃sɛ/	lancai	hurlèrent	/yʀlɛʀ/	hurlairent
lutterai	/lyt(ə)ʀe/	+	sculptais	/skyltɛ/	scùltai
hochez	/ɔʃe/	hochait	échangeait	/eʃɑ̃ʒɛ/	échanjai

5. Writing and Spelling Aloud of 52 Irregular Words (1979)

		Patient's response	
Target word	*Phonetic transcription*	*Writing*	*Spelling aloud*
F < 1			
oignon	/ɔɲɔ̃/	ognon	augnon
album	/albɔm/	albome	albom
damner	/dɑne/	dammé	danné
toast	/tost/	toste	toste
baptême	/batɛm/	bathème	batheme
septième	/sɛtjɛm/	setienne	saitiemme
zinc	/zɛ̃g/	+	zingue
almanach	/almana/	almanat	almana
abdomen	/abdɔmɛn/	+	abtomene
croc	/kʀo/	+	+
jonc	/ʒɔ̃/	jon	jon
acompte	/akɔ̃t/	aconte	acconte
shampooing	/ʃɑ̃pwɛ/	champoin	chempoin
condamnation	/kɔ̃dɑnɑsjɔ̃/	contanation	condanation
condamné	/kɔ̃dane/	condamé	condané
asthme	/asm(ə)/	asme	asme
isthme	/ism(ə)/	isme	istme
agenda	/aʒɛ̃da/	+	+
aluminium	/alyminjɔm/	+	aluminiom
calcium	/kalsjɔm/	+	calsiom
transition	/trɑ̃zisjɔ̃/	+	+
1 ⩽ F ⩽ 30			
solennel	/sɔlanɛl/	solannel	solannel
automne	/ɔtɔn/	automme	hotone
soixante	/swasɑ̃t/	+	soicente
août	/u/	out	+
dixième	/dizjɛm/	dixiemme	disième
sixième	/sizjɛm/	sixiemme	sizième
vingtaine	/vɛ̃tɛn/	vintaine	vintaine
gars	/gɑ/	gas	gas
tabac	/taba/	+	+
chef d'oeuvre	/ʃɛdœvʀ(ə)/	+	chai d'oeuvre
paye	/pɛj/	peil	+
fusil	/fyzi/	+	fusyl
sculpteur	/skyltœʀ/	sculteur	sculteur
alcool	/alkɔl/	alcol	alcol
respect	/ʀɛspɛ/	respec	respec
caoutchouc	/kautʃu/	caoutchou	caoutchou
transaction	/tʀɑ̃zaksjɔ̃/	+	transation
estomac	/ɛstɔma/	+	+
tramway	/tʀamwɛ/	tramwei	tramwvé
nerf	/nɛʀ/	+	+
F ⩾ 31			
femme	/fam/	+	+
monsieur	/məsjø/	messieu	monsié
six	/sis/	+	+
dix	/dis/	+	+
deuxième	/døzjɛm/	+	dexième
second	/s(ə)gɔ̃/	+	segon
pied	/pje/	piet	piet
examen	/ɛgzamɛ̃/	+	examin
gentil	/ʒɑ̃ti/	jentil	janti
aspect	/aspɛ/	aspec	aspec
messieurs	/mesjø/	messieu	messieu

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(*Received March 4, 1980*)

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ARNOLD-CHIARI MALFORMATION

IMPROVEMENT IN EYE MOVEMENTS AFTER SURGICAL TREATMENT

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INTRODUCTION

THE Arnold-Chiari malformation is a congenital anomaly in which the cerebellar tonsils and the lower brain-stem herniate into the cervical canal. The medulla and lower pons are elongated and flattened, and the tonsils are often bound down by arachnoid adhesions (Peach, 1965). Symptoms, which often do not appear until adolescence or adulthood, include ataxia, dysphagia, weakness, headache and visual complaints. Forty (Saez, Burton and Yanagihara, 1976) to sixty (Malis, Cohen and Gross, 1951) per cent of patients presenting for neurosurgical treatment have nystagmus of some type. These patients complain of oscillopsia, diplopia or visual blurring and in some, the visual complaint is the presenting problem (Corhill and Vijagan, 1979).

Although improvement in visual complaints has been reported following sub-occipital decompression (Malis, Cohen and Gross, 1951; Corhill and Vijagan, 1979), to our knowledge there has been no systematic evaluation of eye movement abnormalities in patients with Arnold-Chiari malformation before and after operation. In this report we describe five patients who presented with prominent abnormalities of eye movement. Four of these patients had objective and subjective improvement after operation.

CASE REPORTS

Quantitative evaluation of eye movements is described below in the Results section.

Patient 1.

Five years prior to admission this athletic 22-year-old woman started to have difficulty judging when to strike a tennis ball. She developed occasional diplopia and 'jumping' of objects on lateral gaze three years before admission. Fifteen months prior to admission she attempted ballet lessons but had great difficulty; no matter how hard she tried to fixate on surrounding targets while doing pirouettes, she persistently experienced blurred vision and a sense of imbalance. She was referred to UCLA for evaluation. Examination revealed downbeat nystagmus in the midposition, mild hyperreflexia, increased tone and an equivocal plantar response on the left. Strength, sensation and co-ordination were normal.

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CT scan was normal. Pneumoencephalography (PEG) showed widening of the upper cervical cord and medulla. The ventricular system did not fill with air. A left vertebral angiogram showed the tonsillar branch of the left postero-inferior cerebellar artery coursing below the foramen magnum. A sub-occipital decompression and upper cervical laminectomy were performed. The right cerebellar tonsil extended down to C2. The lower brain-stem was elongated with the fourth ventricle extending into the cervical region. The right cerebellar tonsil compressed and deformed the posterior aspect of the cervical medullary junction.

The patient felt much better by the third month after the operation. She was able to look 30 degrees from the primary position before oscillopsia occurred. She was able to look down to read and started playing tennis again with improved accuracy when hitting the ball. By eight months after the operation activity in sports had increased and reading had returned to normal. She considered herself essentially normal by eighteen months after the operation. She admitted to unsteadiness and visual blurring in activities involving rapid head movements, but they were less than before the operation.

Patient 2

Ten years prior to admission this 26-year-old man started having headaches in the sub-occipital region. They were particularly severe when he cheered loudly at high school basketball games. Flexion of the neck relieved the headaches. He stopped participation in college track five years prior to admission because his running had become inco-ordinated. He stopped reading because the words 'jumped' on the page. He complained that it was almost impossible to follow a moving object with his eyes, saying, 'I can't keep up with it'. He also complained that whenever he turned his head to look at an object he experienced blurred vision for several seconds before the object was recognizable.

On examination he had a midposition downbeat nystagmus, a decreased gag reflex, severe truncal ataxia, hyperactive deep tendon reflexes in the lower limbs and bilateral extensor plantar responses. Sensory and motor examination were normal.

CT scan was normal, but computed tomography of the cervical spine with metrizamide showed that the cerebellar tonsils were in the cervical canal.

Sub-occipital craniectomy and C1-C2 laminectomy were performed. The cerebellar tonsils were descended symmetrically to the upper border of C2. The fourth ventricle was located in the cervical canal. The condition of the lower brain-stem was not described.

The patient continued to have the visual complaints noted above one month after the operation. His gait was slightly improved and dysphagia had resolved. Three months after the operation he was able to walk heel-to-toe with only mild ataxia. He no longer complained of oscillopsia and was able to read. He was able to follow moving targets easier. He still had visual blurring associated with brisk head movement.

Patient 3

This 43-year-old woman developed imbalance on walking one year prior to admission. Intermittent headaches, accentuated by Valsalva manœuvres, began in the vertex. Six months later both legs were weak and she was unable to lift her right arm above her shoulder. Dysphagia with regurgitation of fluids developed. She had two distinct visual complaints. The first, and most prominent, was horizontal 'jumping' of objects which was most severe on lateral gaze. The second complaint involved the inability to turn her head and glance at something quickly and then turn away without a blurring of the object and a transient sense of imbalance. She always had to 'stop and take a second look' to identify the object clearly.

On examination she had a horizontal nystagmus to the left in the primary position, a depressed gag reflex, 3/5 strength in the right arm and 4/5 strength in the lower limbs. Deep tendon reflexes were 2/4 symmetrically with bilateral extensor plantar responses. She had severe truncal ataxia.

CT scan was normal. PEG showed enlargement of the cord outline from the foramen magnum to C3. Air did not enter the fourth ventricle. An angiogram with injection into the left vertebral artery showed inferior displacement of the tonsillar branches of the postero-inferior cerebellar artery.

A sub-occipital craniectomy and C1-C3 laminectomy was performed. The tonsils were descended to the lower border of C2. The fourth ventricle was located in the cervical canal.

Strength improved in the right arm almost immediately after operation. By four days after the operation she was able to walk without assistance and dysphagia had resolved. She continued to have the same visual complaints that she had had before the operation. Her only complaint two months after operation was 'unsteadiness' of gait when she was tired. By five months after operation she felt 'like a new person' and denied any problems. Examination showed only 4 + /5 weakness of the right arm and mild ataxia on walking heel-to-toe.

Patient 4

This 49-year-old woman had a sub-occipital craniectomy and C1-C3 laminectomy seven years previously, after the diagnosis of Arnold-Chiari malformation was made by pneumoencephalography. Her only complaint prior to operation was 'eye strain' when reading characterized by vertical oscillopsia. She had had downbeat nystagmus in the primary position accentuated by downward and lateral gaze but diminished by upward gaze. The rest of the neurological examination was normal. On follow-up evaluations four and six years after the operation the patient showed little improvement in her ocular function. She had learned to compensate for the oscillopsia by tilting her head downward, putting her eyes above the midposition where the nystagmus was diminished or absent.

Patient 5

This 61-year-old woman underwent a sub-occipital craniectomy and cervical laminectomy for Arnold-Chiari malformation twelve years prior to our examination. At operation the tonsils of the cerebellum were descended to C2 and the fourth ventricle was in the cervical canal. For several years prior to operation the patient had had a prompt, severe headache whenever she coughed. She had developed dysphagia and her gait had become unsteady. At the time of operation she had had an intermittent rotatory nystagmus, particularly on left gaze, a decreased gag reflex on the right and ataxia. When we evaluated her twelve years later she considered herself completely normal except for occasional 'dizziness' when dancing. Neurological examination was normal.

METHODS

Eye movements were recorded with D.C. electro-oculography (EOG). Horizontal movements of each eye were recorded by electrodes at the inner and outer canthi and vertical movements were recorded with electrodes placed above the eyebrow and below the lower eyelid. The bandwidth of the recording system was 0 to 35 Hz (− 3 dB). The velocity of the slow components of jerk nystagmus, the velocity of smooth pursuit movements and the peak velocity, amplitude and latency of saccades were calculated by digital computer techniques. Complete details of the recording and analysis systems have been described previously (Baloh and Honrubia, 1979; Baloh, Langhofer, Honrubia and Yee, 1980).

Spontaneous nystagmus was recorded with the patient fixating on a target in the centre of the visual field, 30 degrees up and 30 degrees down and at 30 degrees to the right and left of each of these three positions.

Saccades and smooth pursuit were induced by asking the patient to track a laser target projected on to a screen directly in front of the patient. For saccades the target moved in a stepwise fashion of random amplitude and random interval between jumps. For smooth pursuit the target moved horizontally and vertically in a sinusoidal pattern (frequency 0.2 Hz and 0.4 Hz, peak velocity 22.5 and 45 deg s^{-1} respectively).

Horizontal optokinetic responses were obtained with the patients seated within a cloth drum of 1 m diameter whose interior consisted of alternating black and white vertical stripes. Rotation of the drum produced stimulation of the entire visual field. The drum was rotated in a sinusoidal pattern (frequency 0.05 Hz, peak velocities 30 and 60 deg s^{-1}).

The horizontal vestibulo-ocular reflex was tested by sinusoidally rotating the patients on a motorized chair in the dark and in the light with a fixation point directly in front of them (0.05 Hz, peak velocities 30 and 60 deg s^{-1}).

RESULTS

Spontaneous Nystagmus

Patients 1, 2 and 3 were tested before and after operation while Patients 4 and 5 were only tested after operation. Fig. 1 graphically illustrates the course of change in nystagmus in the first three patients.

Before operation Patients 1 and 2 had downbeat nystagmus of 1 to 2 degrees amplitude in the primary position. The nystagmus in the primary position disappeared intermittently for several seconds during the two-hour test session. The downbeat nystagmus was always present and most prominent (3 to 4 degrees amplitude) in the lateral gaze positions where it also had a small amplitude (1 to 2

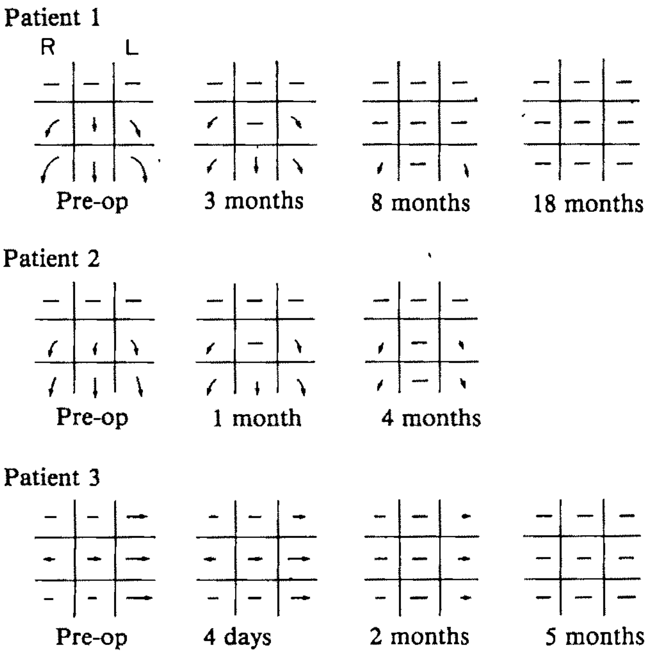

FIG. 1. Pre- and post-surgical nystagmus patterns. The arrows indicate the relative amplitude and direction of nystagmus in primary position and 30 deg eccentric gaze.

degrees) horizontal component in the direction of gaze. Thirty degrees upward gaze abolished the nystagmus in both patients. Patient 3 (fig. 1) had a horizontal nystagmus of 1 to 2 degrees amplitude beating to the left in the primary position. It increased in amplitude (2 to 3 degrees) on 30 degrees gaze to the left and changed to a right beating nystagmus (amplitude 1 degree) with 30 degrees gaze to the right. Based on clinical descriptions prior to operation, Patient 4 had prominent downbeat nystagmus in all fields of gaze (including upward gaze), and Patient 5 had rotatory nystagmus on lateral gaze in either direction but no nystagmus in the primary position.

After surgical decompression, Patients 1, 2, 3 and 5 had gradual resolution of the nystagmus. Patient 2 no longer had nystagmus in the primary position one month after operation. Patients 1 and 3 were not tested until the third and second months after operation, respectively, but at that time the nystagmus in the primary position had resolved. Subsequent improvement in Patients 1, 2 and 3 was characterized by decreasing nystagmus at greater and greater degrees of gaze deviation. Nystagmus resolved completely in Patients 1 and 3 by eighteen months and five months, respectively. The last time we tested Patient 2, four months after operation, he had downbeat nystagmus of 1 degree amplitude on 30 degrees lateral gaze only. Patient 4 was tested four and seven years after operation and each time there was prominent downbeat nystagmus of 2 to 3 degrees amplitude in all gaze positions except 30 degrees upward gaze, where it decreased to 1 to 2 degrees amplitude. Patient 5 did not have nystagmus twelve years after operation.

Smooth Pursuit and Optokinetic Nystagmus (OKN)

Before operation, smooth pursuit (horizontal and vertical) and OKN were impaired in Patients 1, 2 and 3 (figs. 2 and 3, upper traces) and in Patient 4 by clinical description; smooth pursuit and optokinetic nystagmus in Patient 5 were not reported. Measurement of gain (peak eye velocity/peak target velocity) of horizontal smooth pursuit and optokinetic nystagmus (Table 1) reflect the patients' poor performance before operation at low and high target velocities. Upward and downward vertical pursuit were impaired in Patients 1 and 2 at both target velocities, but downward pursuit was consistently worse than upward pursuit. Vertical pursuit was symmetrically impaired in Patient 3.

After operation horizontal smooth pursuit and optokinetic nystagmus improved markedly in Patients 1, 2 and 3 (Table 1; figs. 2 and 3, lower traces). Smooth pursuit at the lower target velocity returned to normal (that is, within two standard deviations of the normal mean) in Patients 1 and 3. In Patient 2, smooth pursuit to the left returned to normal at the lower target velocity but it remained abnormal to the right three months after operation (although it was still improved from before operation). Smooth pursuit improved at the higher target velocities, but only Patient 3 achieved normal gain by the time of the last testing. Vertical smooth pursuit improved slightly in Patients 1 and 2, but downward pursuit was still worse than upward pursuit. Patient 4 still had severely impaired vertical smooth pursuit

TABLE 1. GAIN MEASUREMENTS (PEAK EYE VELOCLTY/PEAK TARGET VELOCITY) OF HORIZONTAL EYE MOVEMENTS IN PATIENTS WITH ARNOLD-CHIARI MALFORMATION

	Smooth pursuit				*Optokinetic nystagmus*				*Fixation suppression*			
	*0.2 Hz, 22°/s **(0.96 ± 0.05)		0.4 Hz, 45°/s (0.91 ± 0.07)		0.05 Hz, 30°/s (0.94 ± 0.11)		0.05 Hz, 60°/2 (0.84 ± 0.10)		0.05 Hz, 30°/s (0.01 ± 0.01)		0.05 Hz, 60°/s (0.03 ± 0.04)	
	****L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*
Patient 1												
Pre-op.	****0.80	0.53	0.42	0.24	0.50	0.24	0.18	0.09	—	—	0.67	0.58
Post-op. (18 m)	0.98	0.93	0.38	0.45	—	—	0.55	0.40	—	—	0.50	0.25
Patient 2												
Pre-op.	0.46	0.39	0.35	0.22	0.33	0.27	0.07	0.08	0.80	0.60	0.75	0.67
Post-op. (3 m)	0.88	0.72	0.56	0.36	0.60	0.50	0.30	0.17	0.60	0.43	0.73	0.67
Patient 3												
Pre-op.	0.15	0.37	0.29	0.43	0.17	0.50	0.25	0.42	0.13	0.17	0.08	0.17
Post-op. (5 m)	0.98	0.85	0.90	0.64	0.83	0.83	0.67	0.67	0	0	0.03	0.03
Patient 4												
Post-op. (7 y)	0.92	0.74	0.62	0.47	—	—	—	—	—	—	—	—
Patient 5												
Post-op. (12 y)	0.83	0.86	0.41	0.38	0.67	0.67	0.58	0.55	0.13	0.13	0.13	0.17

* Frequency, peak velocity of sinusoidal stimulation. ** Mean gain ± 1 SD from 20 normal subjects with age range similar to that of the patients. *** Direction of pursuit or slow phase eye movement. **** Best gain of at least 3 cycles of sinusoidal stimulation. On any given test session the gain from cycle to cycle did not vary by more than 0.15 (*see* figs. 2 and 3).

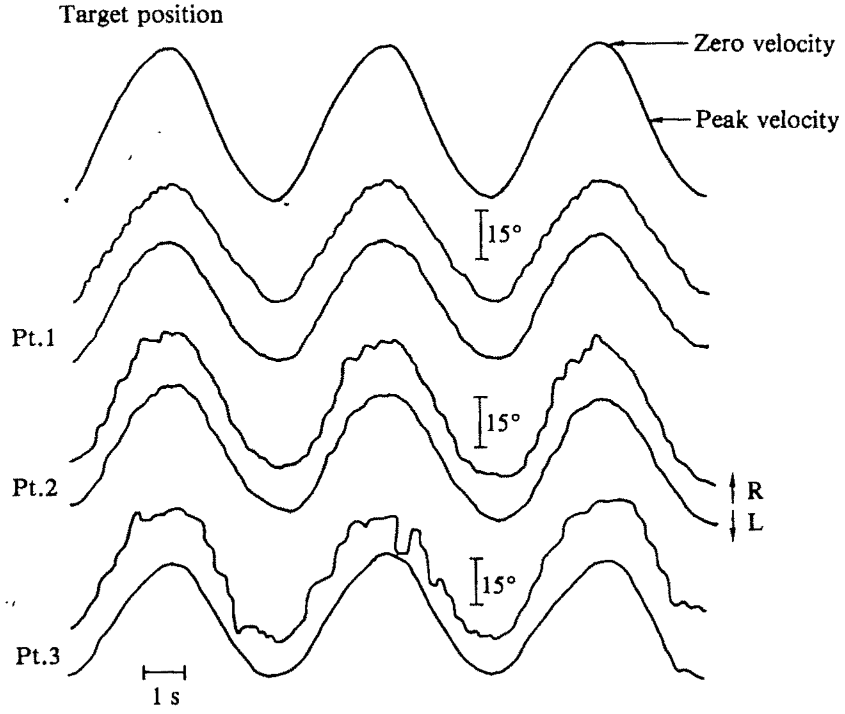

FIG. 2. Horizontal smooth pursuit of a target moving sinusoidally (0.2 Hz, peak velocity 22.5 deg/s) before (*upper traces*) and after (*lower traces*) operation in Patients 1, 2 and 3 (eighteen, three and five months, respectively).

(downward pursuit worse than upward pursuit) and moderately impaired horizontal smooth pursuit at the higher target velocity. Patient 5 had normal horizontal smooth pursuit and nearly normal optokinetic nystagmus at the lower target velocities but not at the higher target velocities.

Fixation Suppression of Vestibular Nystagmus

All five patients generated normal horizontal vestibular nystagmus when they were sinusoidally rotated in the dark (before and after operation in Patients 1, 2 and 3). However, before operation, when Patients 1, 2 and 3 were rotated with a fixation point, they were unable to inhibit horizontal vestibular nystagmus (Table 1). After operation fixation suppression of vestibular nystagmus improved in Patients 1 and 2, and returned to normal in Patient 3. Patient 4 continued to have severely impaired fixation suppression seven years after operation (by visual inspection), and Patient 5 had mildly impaired fixation suppression twelve years after operation.

Saccades

Saccade latency, accuracy and peak velocity were normal in all five patients except Patient 1 who had hypermetric saccades to the left which resolved five months after operation.

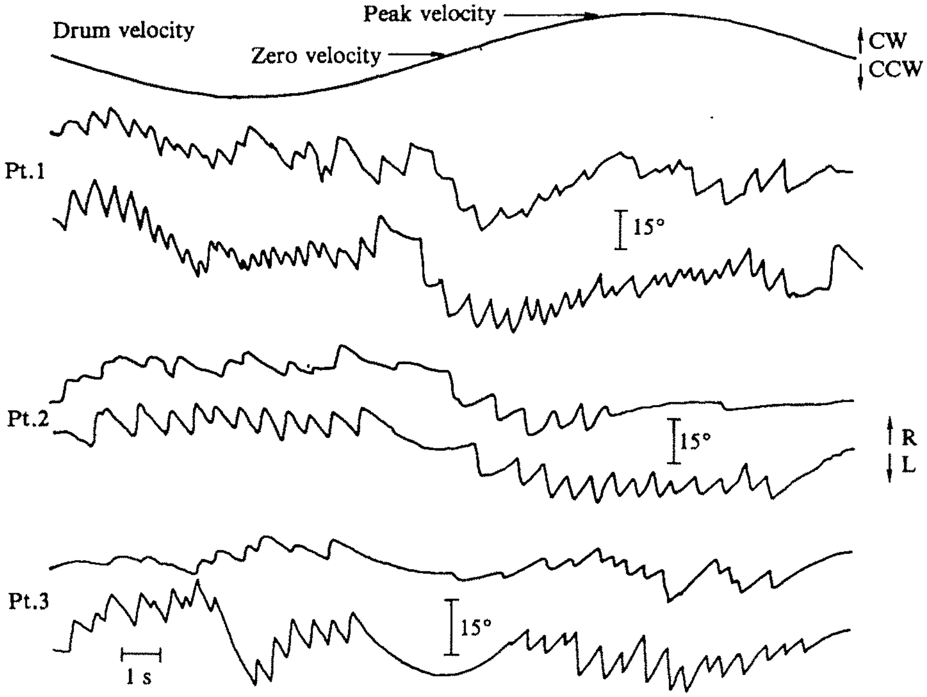

FIG. 3. Horizontal optokinetic nystagmus (0.05 Hz) before (*upper traces*) and after (*lower traces*) operation in Patients 1, 2 and 3 (eighteen, three and five months, respectively). Peak drum velocity was 60 deg s^{-1} for Patient 1 and 30 deg s^{-1} for Patients 2 and 3. CW = clockwise. CCW = counterclockwise.

DISCUSSION

We found that pathological nystagmus and impaired visual-ocular control due to Arnold-Chiari malformation can be improved by surgical decompression. Objective recovery correlated with subjective visual improvement. All our patients complained of oscillopsia, as do most patients with acquired nystagmus from any cause. Oscillopsia can interfere with important functions, such as reading or detailed work, even if the amplitude or frequency of the nystagmus is low. Oscillopsia is particularly incapacitating when nystagmus is present in the primary position or in the first 30 degrees of gaze. If nystagmus is present only at the extremes of gaze, the patient can avoid oscillopsia most of the time. Three of our patients had complete resolution of nystagmus and one patient (Patient 2) had near-complete resolution by four months after operation. We expect the latter patient will eventually fully recover. The patient who still had prominent downbeat nystagmus seven years after operation may have had some improvement, though we could not verify this quantitatively. Since the nystagmus was diminished in upward gaze, she had learned to tilt her head down when looking at targets straight ahead. She felt that the degree of tilting necessary to reduce the oscillopsia was less than before the operation.

Typically, the nystagmus in the primary position resolved first, followed by gradual resolution of the nystagmus on lateral gaze over several months. This is not surprising since before operation the nystagmus was most prominent on lateral gaze in all five patients. Downbeat nystagmus typically increases on lateral gaze (Baloh and Spooner, 1981). The mechanism or anatomical substrate for downbeat nystagmus is not known. Zee, Friendlich and Robinson (1974) suggested that it was due to a selective involvement in downward smooth pursuit, resulting in a tonic imbalance in the vertical smooth pursuit system. However, based on our study (Baloh and Spooner, 1981) of seventeen patients with downbeat nystagmus, we concluded that downbeat nystagmus is a type of central vestibular nystagmus.

Patients 1, 2, 4 and 5 continued to complain of transient blurring of fixated targets during or immediately after their heads were in motion. We believe this was due to the impaired fixation suppression of vestibular nystagmus induced by head rotation. Whenever they turned their heads briskly to glance at something, a burst of vestibular nystagmus occurred causing visual blurring. The nystagmus did not last long enough to be interpreted as oscillopsia. Smooth pursuit also remained impaired in these patients, which is consistent with previous observations that deficits in fixation suppression accompany deficits in smooth pursuit (Troost, Dell'Osso and Daroff, 1976; Dichgans, von Reutern and Rommelt, 1978. Smooth pursuit and fixation suppression of vestibular nystagmus are mediated, at least in part, by the flocculus of the cerebellum. Lisberger and Fuchs (1978) showed that Purkinje cell simple spike firing rate in the flocculus of the monkey is modulated during sinusoidal smooth pursuit and fixation suppression of vestibular nystagmus induced by rotation. On the other hand, rotation in the dark has little effect on Purkinje cell firing rate. Furthermore, ablation of the flocculus impairs fixation suppression in monkeys (Takemori and Cohen, 1974; Zee, Yamazaki and Gucer, 1978). Since the Arnold-Chiari malformation involves cerebellar and lower brain-stem compression, it seems reasonable to assume that failure to completely recover normal fixation suppression and smooth pursuit after operation was due to permanent damage of the flocculus or flocculo-vestibular connections.

Our findings suggest that the abnormalities of eye movement in the Arnold-Chiari malformation are due to compression of the herniating cerebellum against the caudal brain-stem and not a congenital aberrancy of oculomotor pathways. This could explain why patients often do not become symptomatic until adolescence or adulthood. Presumably, compression increases until adaptive limits are exceeded and symptoms appear. The intermittent absence of nystagmus in the primary position observed in Patients 1, 2 and 3 before operation may have been due to transient relief of compression from phsiological factors. Surgical decompression reverses the progression of symptoms if permanent damage has not already occurred. One should recognize that improvement after operation occurs over months, and thus it is premature to assign a poor surgical outcome to a patient who does not show recovery immediately after operation.

SUMMARY

We studied abnormalities of eye movement in five patients with Arnold-Chiari malformation before and after suboccipital decompression. Before operation all patients complained of oscillopsia at rest and visual blurring of fixated targets during and immediately after their heads were in motion. Three patients had downbeat nystagmus, one patient had horizontal nystagmus in the primary position and on eccentric gaze and one patient had rotatory nystagmus on lateral gaze only. Smooth pursuit, optokinetic nystagmus and fixation suppression of vestibular nystagmus were markedly impaired.

Within two months after operation nystagmus in the primary position had resolved in three patients, and four had complete to near-complete resolution of nystagmus in all gaze positions over subsequent months. Oscillopsia decreased concurrently, affording significant functional visual improvement. One patient had only slight functional improvement and continued to have prominent nystagmus seven years after operation. Smooth pursuit, optokinetic nystagmus and fixation suppression of vestibular nystagmus improved in all patients, but none had complete recovery at the higher velocities of stimulation. They still complained of visual blurring associated with head motion, probably due to the poor fixation suppression of vestibular nystagmus.

Our findings suggest that abnormalities of eye movement in Arnold-Chiari malformation are due to compression of the herniating cerebellum against the caudal brain-stem and not a congenital aberrancy of oculomotor pathways.

Nystagmus resolved more readily than pursuit or fixation suppression abnormalities, but most patients showed gradual improvement in all abnormalities four months after operation.

ACKNOWLEDGEMENTS

The authors would like to thank Drs Eugene Stern and Leslie Cahan, Neurosurgery Department, UCLA, for permission to examine their patients, Ms Susan Sakala and Ms Kathleen Brintnall for technical assistance and Mrs Karen Einstein for editorial assistance. This study was supported by NIH Grants NS 07059 and NS 09823.

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(*Received March 18, 1980*)

ADDENDUM: Since this manuscript was prepared another report has been published of a patient with Arnold-Chiari malformation whose primary position downbeat nystagmus resolved after sub-occipital decompression (Pedersen, R. A., Troost, B. T., Abel, L. A. and Zorub, D. (1980) Intermittent downbeat nystagmus and oscillopsia reversed by sub-occipital craniectomy. *Neurology, Minneapolis,* **30**, 1239-1242).

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FAMILIAL DEMENTIA OF ADULT ONSET WITH PATHOLOGICAL FINDINGS OF A 'NON-SPECIFIC' NATURE

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INTRODUCTION

ALTHOUGH the number of disorders that can produce dementia in adult life is quite large (Haase, 1977), there are relatively few which have the capacity to do so in familial fashion (Torack, 1978). Varieties of familial dementia of adult onset that are well characterized clinically and pathologically include familial multi-infarct dementia (Sourander and Wålinder, 1977), the senile dementia-Alzheimer disease complex (Cook, Ward and Austin, 1979), congophilic angiopathy (Torack, 1978), Wilson's disease, Huntington's disease, Creutzfeldt-Jakob disease (Ferber, Wiesenfeld, Roos, Bobowick, Gibbs and Gajdusek, 1974; Masters, Harris, Gajdusek, Gibbs, Bernoulli and Asher, 1979; Masters, Harris, Gajdusek, Gibbs, Bernoulli and Asher, 1980) and Pick's disease (Schenk, 1959). In addition, there are other, more vaguely defined dementing disorders, such as progressive subcortical gliosis (Neumann and Cohn, 1967) and so-called Kraepelin's disease (Schaumburg and Suzuki, 1968), that may affect more than one member of a family.

We report a family in which 4 (possibly 5) of 10 siblings developed dementia in middle or late life. Post-mortem examination was performed on 3. Upon careful analysis of the clinical and pathological findings, we find ourselves unable to assign this condition diagnostically to any of the well-recognized categories of familial dementia.

REPORT OF CASES

The pedigree of the family described below is indicated in fig. 1. Both parents immigrated to central New York from Italy in the early part of this century. Neither the mother, who died at 72 years of heart disease, nor the father, who died at 56 years of diabetes mellitus, showed any sign of mental impairment or senility during life. Little is known of other relatives (especially those in Italy) except that neither of the father's two sisters, both of whom died in their 70s, were demented.

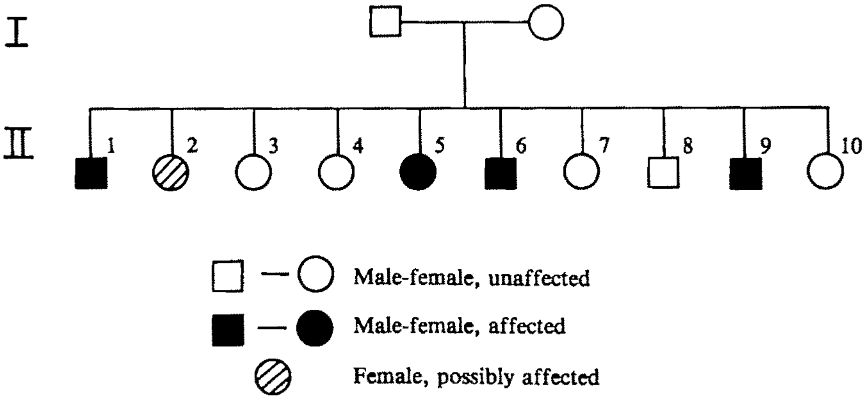

FIG. 1. Family pedigree.

The family is remarkably close-knit, and there has been much intrafamilial contact. All ten children have remained in or near their city of birth. None of the living siblings (II-3, aged 72 years; II-4, aged 71 years; II-7, aged 64 years; II-8, aged 64 years; and II-10, aged 59 years) have shown any sign of dementia. Of those who were demented, II-9 was the first to have been affected. Interestingly, II-1, II-5 and II-6 all began to show evidence of mental dysfunction within a six-month period, approximately eight to nine years after the onset of illness in II-9.

As far as can be determined, no member of the family has ever consumed raw meat, raw seafood or brain material. The family was reared in an urban household and had limited contact with animals, although dogs were frequent pets for II-9. Nor has anyone developed an interest in fishing or hunting. Several members have worked at many different jobs, but none has ever worked as a butcher or in any capacity necessitating exposure to wild animals.

Case II-1

The behaviour of this man, a retired clerk, began to change around the age of 68 years. He became depressed and intermittently belligerent, would not eat or go out of the house, showed little concern for his personal appearance (refusing to bathe or shave) and developed urinary and fæcal incontinence. Progressive deterioration necessitated involuntary admission to a state psychiatric institution at the age of 69 years. He had received no medications up to this time.

Examination on admission showed his speech to be normal, although verbal productivity seemed diminished. He was coherent and relevant and could express ideas in a simple way. Affect was labile, and he shifted rapidly from a crying to a smiling state. He was fairly orientated to person and place but not at all to time. Recent and remote memory were poor and patchy. Auditory memory span was poor. Abstractive ability (proverb interpretation) was adequate, but counting and calculation were weak, as evidenced by inability to do serial 7s past 79. General fund of knowledge was fair considering his seventh-grade level of education but his over-all intelligence was judged to be dull average. He showed no insight, and his judgement was notably impaired. He had difficulty buttoning and unbuttoning his shirt because of tremulousness of the hands and slowness of movement. Cogwheel rigidity, a mask-like facial expression and a steppage gait were also noted.

Full blood count, urinalysis, blood chemistries, serological tests for syphilis and x-rays of the chest and skull were within normal limits. An electroencephalogram (EEG) was interpreted as normal.

In hospital, he was started on haloperidol, 5 mg daily, and imipramine hydrochloride, 75 mg daily.

The haloperidol was maintained for five months and the imipramine for approximately two years. From the fifth to seventeenth months he also received thioridazine hydrochloride, 50 mg daily. No medications were given, however, after the second year of his being in the institute. His mental state and capacity for self-care steadily declined. He became aphasic and bedridden, developed flexion contractures and a strong grasp reflex, lost over 45 kg and suffered intermittently from bedsores, anæmia and respiratory infection. He died at the age of 74 years, approximately six years after the onset of dementia.

Bilateral bronchopneumonia, generalized atherosclerosis and old myocardial infarction were the principal findings at general autopsy.

The formalin-fixed brain weighed 975 g. The arteries at the base were mildly to moderately atherosclerotic. There was widespread cerebral atrophy, especially frontally, as evidenced by marked gyral narrowing and sulcal widening (fig. 2). The cerebral white matter was considerably reduced in volume, and the lateral ventricles were moderately enlarged. The basal ganglia and thalamus were small but of normal contour. Because of the presence of a rather marked degree of post-mortem handling artefact, the midbrain and substantia nigra could not be properly evaluated in the gross, but the lower brain-stem and cerebellum appeared to be normal.

On histological examination, the most striking finding was the presence of widespread, moderately severe loss of nerve cells from the cerebral cortex. Astrocytosis, though present focally, did not appear to be commensurate with the neuronal loss. Also noteworthy was the presence of status spongiosus, that is, vacuolization of the neuropil with widening of perineuronal spaces. At sites of

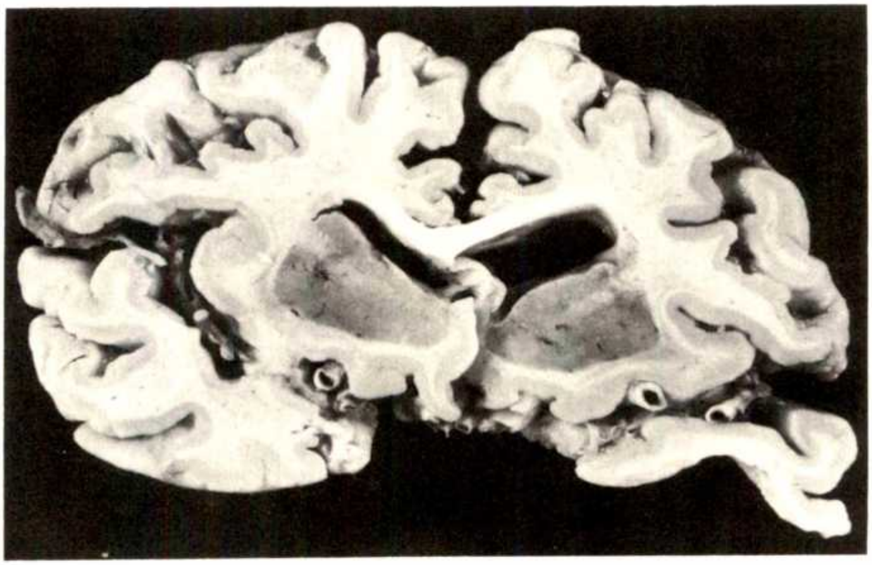

FIG. 2. *Case II-1.* Coronal section of brain showing profound cerebral atrophy. Atherosclerosis of the arteries at the base is also evident.

severe involvement, such vacuolization was often noted both superficially and deep within the cerebral cortex; where the pathological changes were less severe, however, it seemed markedly accentuated within the second or second and third cortical layers (fig. 3). Many of the remaining neurons exhibited hyperchromasia and widening of pericellular spaces to such a degree as to impart a scalloped or 'spiky' configuration to these cells. These changes were most obvious in the frontal lobes, but the temporal and parietal cortex were affected in similar fashion, albeit less severely. The occipital cortex, however, appeared to be nearly normal. No senile plaques, neurofibrillary tangles, granulovacuolar degeneration, ballooned neurons or argyrophilic Pick inclusion bodies were seen. The subcortical white matter showed variable degrees of pallor and rarefaction, especially frontally, where occasional small perivascular accumulations of lipid-laden macrophages and moderate loss of myelinated axons were noted. Widening of perineuronal spaces similar to that described in the cerebral cortex was also observed in the striatum, in the globus pallidus and in Sommer's sector of the hippocampus. The thalamus,

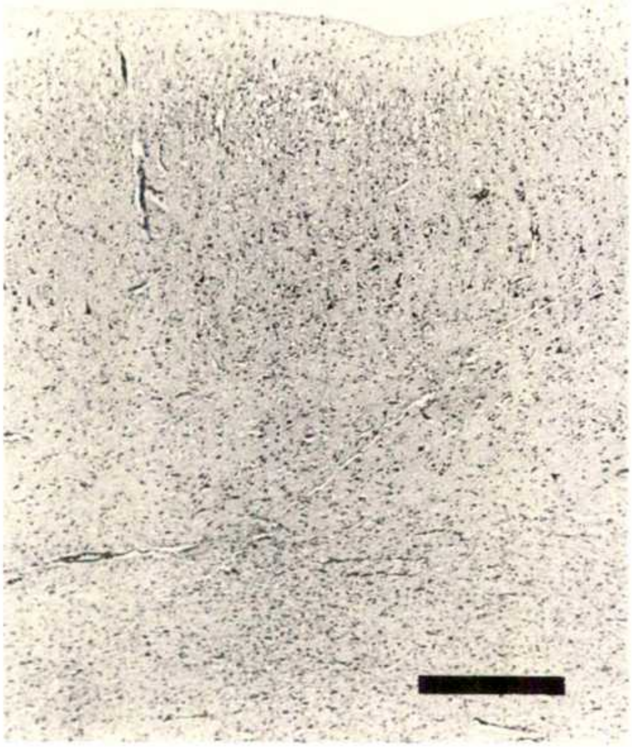

FIG. 3. *Case II-1.* Frontal cortex showing reduction in calibre and microcystic rarefaction in layer 2. Hæmatoxylin and eosin. Bar = 500 μm.

hypothalamus, subthalamic nucleus, red nucleus, substantia innominata, and amygdala showed no specific pathological change. Those portions of the substantia nigra that were identified in tissue sections contained richly neuromelanized nerve cells without reactive change and without Lewy body formation. No abnormalities were noted within the pons, medulla or cerebellum.

Case II-2

This lady died at the age of 68 years while in hospital for a bladder operation. Although she had never undergone formal neurological evaluation, her husband was said to have complained that she had been quite forgetful for an ill-defined period prior to her death. Autopsy was not performed.

Case II-5

This lady, a retired factory worker, was admitted to hospital at the age of 63 years for forgetfulness (as manifested particularly by a tendency to misplace household objects), inappropriate behaviour and hyperphagia (resulting in a gain in weight of 18 kg) of approximately one year's duration. On admission she was alert and fully orientated, but her attention span was short, and she was inappropriately tearful at times. She made many errors when attempting serial 7s; she was able to recall only 3 of 5 items after a five-minute interval; she could produce only two four-letter words beginning with the letter 'C'; and she interpreted proverbs literally. The remainder of the neurological examination was normal.

Routine laboratory studies, including blood count and serum chemistries, were within normal limits. Pneumoencephalography (PEG) revealed mild symmetrical enlargement of the lateral and third ventricles, without evidence of obstruction; there was also a suggestion of bilateral cerebral cortical atrophy, particularly in the insular regions. Gamma-cisternography was slightly abnormal, with transient ventricular filling and evidence of complete development over the cerebral convexity at twenty-four hours. Technetium-99 m brain scan was normal.

Following discharge, she continued to deteriorate and was admitted to a state psychiatric institute at the age of 64 years. At this time she was temporally disorientated and could not name the President of the United States or the Governor of New York. A slow, wide-based gait was also noted. Over the ensuing year she became doubly incontinent and required total nursing care. She lost 14 kg. Grasp reflexes appeared, and she became almost totally mute. By the end of the second year of institute care, she developed severe spastic paraplegia. One examiner noted that the contour of the left side of the face was smoothed out and that the right plantar was extensor. By the end of the fourth year she required intermittent nasogastric tube feedings. She died at the age of 68 years, approximately six years after the onset of dementia, in a mute, rigid, emaciated state.

At no time during the course of illness did she receive medication for her neurological condition.

The only noteworthy finding at general autopsy was bilateral bronchopneumonia.

The brain weighed 925 g after formalin fixation. The cerebral arteries and their major branches were free of atherosclerosis. The most striking gross abnormality was the presence of severe convolutional atrophy affecting all parts of the frontal lobes and, to a lesser extent, the anterior parietal and temporal lobes (fig. 4). The cerebral white matter was considerably reduced in volume. The frontal horns of the lateral ventricles were prominently enlarged and their dorsolateral angles blunted. The basal ganglia and thalamus, though of small size, were of normal configuration.

Microscopic examination confirmed the gross impression of reduced cerebral cortical thickness, particularly in the frontal lobes. Where most severe, the tissue

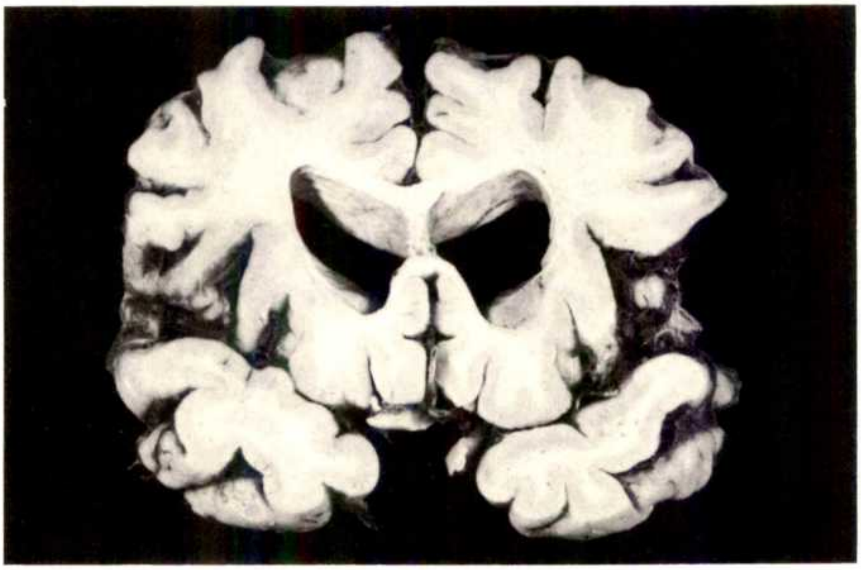

FIG. 4. *Case II-5.* Coronal section of cerebral hemispheres showing severe atrophy and ventricular enlargement.

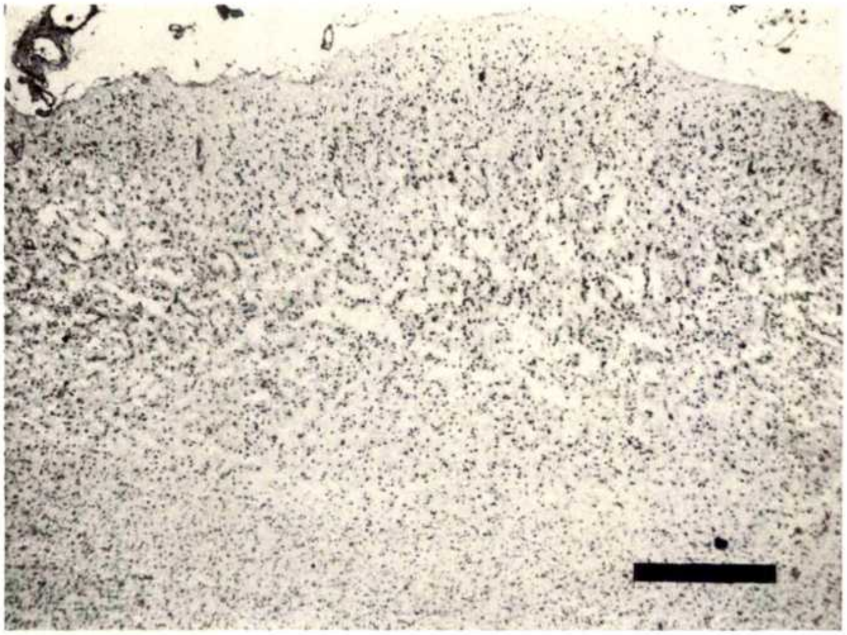

FIG. 5. *Case II-5.* Frontal cortex showing reduction in calibre and rarefaction and splitting of the tissue throughout. Hæmatoxylin and eosin. Bar = 500 μm.

was pale and rarefied, and characterized by moderately severe nerve cell loss and astrocytosis (fig. 5). There was considerable regional variation in the intensity of the pathological process. In less severely affected areas vacuoles of moderate size and widened perineuronal spaces (status spongiosus) were particularly prominent within the second and third cortical layers. Many of the remaining neurons, particularly the larger pyramidal cells, showed slight irregularity of configuration, increased lipochrome pigment content, and enhanced staining density. The frontal cortex appeared to be more severely diseased than the parietal or temporal cortex; the occipital cortex was largely spared, although occasional small foci of rather intense involvement could be identified. The white matter underlying the most severely affected areas showed moderate loss of myelinated axons and reactive astrocytosis. Within the hippocampus there was focal microcystic rarefaction which was restricted to Sommer's sector; this consisted mainly of marked widening of perineuronal spaces in such a manner as to cause the pyramidal nerve cells to assume a scalloped contour (fig. 6). No senile plaques, neurofibrillary or granulovacuolar degeneration, or intracytoplasmic Pick inclusion bodies were noted. The caudate nucleus and putamen showed severe widespread pallor and rarefaction (microcystic in places), with moderately severe, focally intensified nerve cell loss and astrocytosis. Although no systematic attempts at quantification were made, the impression was gained that the loss of small nerve cells was greater than the loss of large nerve cells.

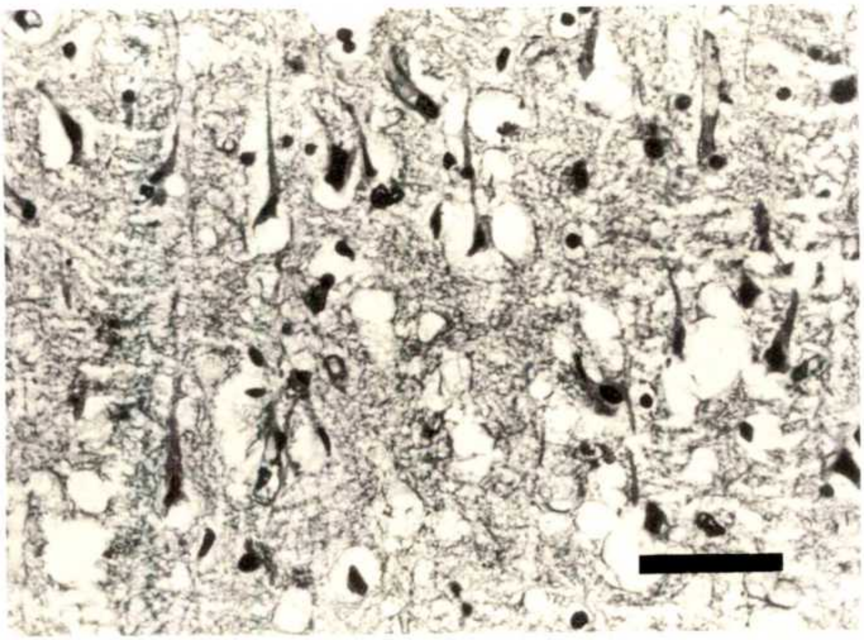

FIG. 6. *Case II-5.* Sommer's sector of the hippocampus showing widening of perineuronal spaces and hyperchromasia and irregularity of configuration of nerve cells. Bodian. Bar = 50 μm.

There was also a reduction in the staining density of the bundles of myelinated fibres coursing through these nuclei. The globus pallidus, amygdala, hypothalamus, subthalamic nucleus, red nucleus and substantia nigra were spared, but focally severe nerve cell loss and astrocytosis were seen in the dorsomedial nucleus of the thalamus. In the brain-stem, there was pallor, rarefaction and reactive astrocytosis within the corticospinal tracts. There was a suggestion of mild Purkinje cell loss and proliferation of Bergmann astrocytes within the cerebellar cortex; status spongiosus, however, was not seen.

Case II-6

This man, a labourer, entered the hospital at the age of 62 years with a one-year history of progressive dementia. His wife observed that he had begun to 'slow down', that his memory was deteriorating and that he suffered occasional urinary incontinence. On examination, he recalled his date of birth but he could not name any Presidents. He was unable to do serial 7s. He was able to repeat 5 digits but not 6. Memory retention, however, was poor; he could recall only 1 of 3 objects after two minutes. He was very poor at copying diagrams. He showed no insight into the nature of his illness. Palmomental reflexes were elicited on both sides, but the plantars were flexor. Heel-to-toe walking was slightly unsteady. Cranial nerve, sensorimotor and equilibratory function were intact.

Routine laboratory studies, including blood count, blood chemistries and examination of the cerebrospinal fluid, were within normal limits. The EEG was slow and poorly organized, without evidence of paroxysmal, focal or lateralizing activity. Technetium-99 m brain scan showed diminished perfusion in the territory of supply of the left middle cerebral artery. Gamma-cisternography revealed a large collection of radiopharmaceutical over the cerebral cortex on either side, more marked on the left; no ventricular filling was seen. PEG disclosed mild enlargement of the lateral and third ventricles and widening of sulci over both frontal and anterior parietal areas.

Outpatient neurological re-evaluation at the age of 63 years showed that his dementia had progressed. He had difficulty finding words and would point rather than ask for what he wanted. He had also become noticeably less inhibited in his relationship with his wife. He showed little or no understanding of the conversations being held before him.

When seen at the age of 64 years, he walked with an unsteady, shuffling gait. He spoke very little and had great difficulty understanding directions.

He was cared for at home until the age of 66 years, when he was admitted to a local hospital for fever, nausea and vomiting. X-rays of the chest showed bilateral pneumonia. Despite fluid and antibiotic therapy he died on the third hospital day, five years after the onset of dementia.

At no time did he receive medication for his neurological illness.

Bilateral bronchopneumonia, hæmorrhagic infarction of the small intestine and moderately severe generalized atherosclerosis were the major findings at general autopsy.

The formalin fixed brain weighed 1040 g. The vessels at the base were free of atherosclerosis. There was striking, widespread cerebral convolutional atrophy, particularly in the frontal and perisylvian areas, and less notably in the temporal and parietal lobes (fig. 7). The cerebral white matter seemed greatly reduced in volume. The lateral ventricles, especially the frontal horns, were diffusely and moderately enlarged, as was the third ventricle. The striatum appeared to be reduced in size, more so rostrally. The mammillary bodies were small. Except for mild reduction in the intensity of pigmentation of the substantia nigra, the brain-stem and cerebellum were of normal gross appearance.

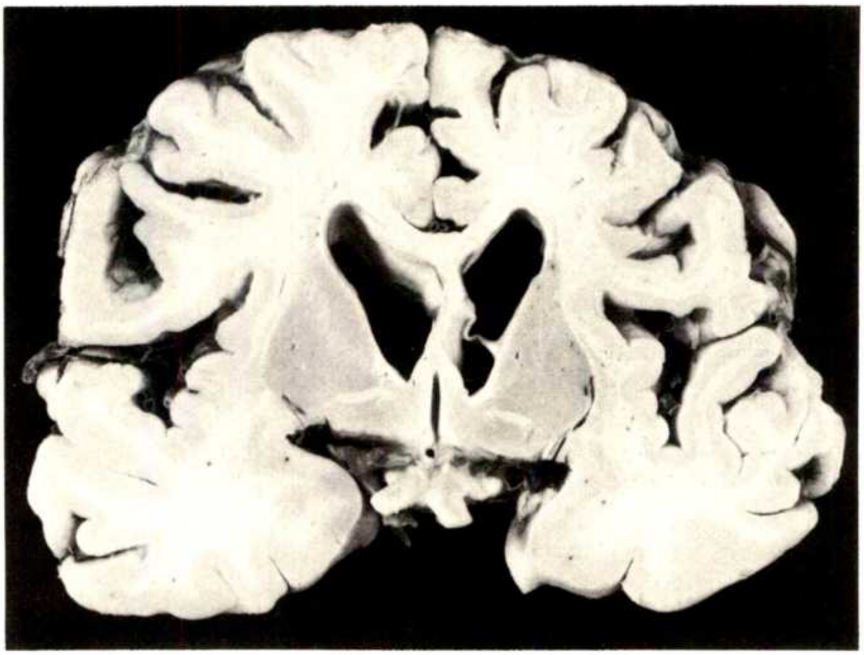

FIG. 7. *Case II-6*. Coronal section of cerebrum showing widespread atrophy.

Histologically there was widespread reduction in the thickness of the cerebral cortex, particularly frontally; the temporal and parietal cortex were less severely involved, and the occipital cortex was affected little if at all. At sites of maximal damage there was severe nerve cell loss and astrocytosis affecting all cell layers. Equally striking was the presence of generalized, focally intensified pallor of staining and rarefaction affecting predominantly, and almost in circumscribed fashion, the outer two to three layers of the cerebral cortex. Vacuolization of the neuropil and widening of perineuronal spaces (status spongiosus) was particularly evident within though not limited to layers 2 and 3 (fig. 8). Many of the nerve cells that remained, such as the larger pyramidal cells, showed increased staining density (in part due to the intracellular accumulation of lipochrome pigment) and irregularity of configuration; their margins were often indented by perineuronal vacuoles of moderate size (fig. 9). In less severely diseased portions of the cerebral cortex, vacuolization was less obvious or more irregularly distributed, although pallor of staining of the outer layers was still noteworthy; astrocytosis, when present, was largely confined to the deepest layers (fig. 10). The severity of involvement of the underlying white matter was proportional to the extent of disease within the cortex; in the convolutional white matter of the frontal lobes, for example, pallor of myelin staining, reduction in axonal density, and reactive astrocytosis, were quite marked. Lipid-laden macrophages, however, as seen in oil-red-O-stained frozen sections, were not very numerous, either within the white matter or within the cerebral cortex.

Within Sommer's sector of the hippocampus there was a partial loss of nerve cells and an accompanying proliferation of mildly hypertrophied astrocytes. Although occasional Hirano bodies were seen, no granulovacuolar degeneration was identified; nor were senile plaques, neurofibrillary tangles, ballooned neurons or argyrophilic Pick inclusion bodies noted either here or within the cerebral cortex. There was a mild to moderate loss of nerve cells (predominantly small neurons) and reactive astrocytosis within the striatum (fig. 11). Neuronal loss and astrocytosis were also seen within the dorsomedial nucleus of the thalamus (fig. 12). The globus pallidus, subthalamic nucleus, red nucleus, hypothalamus (including mammillary bodies), substantia innominata and substantia nigra appeared to be within normal limits. No microscopic abnormalities were identified within the brain-stem or cerebellum; in particular, there were no foci of status spongiosus within the cerebellar cortex.

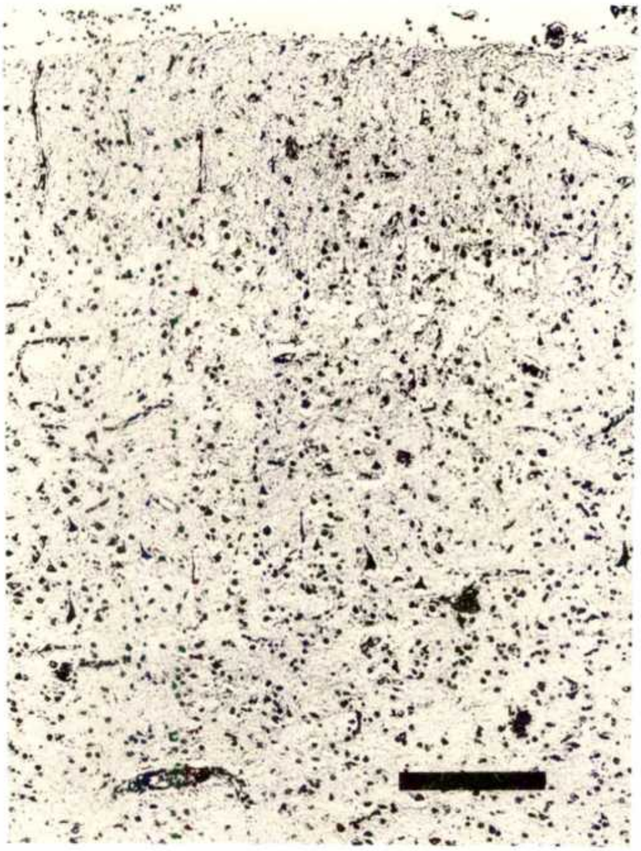

FIG. 8. *Case II-6*. Frontal cortex showing reduction in calibre and microcystic rarefaction, especially in layers 2 and 3. Hæmatoxylin and eosin. Bar = 200 μm.

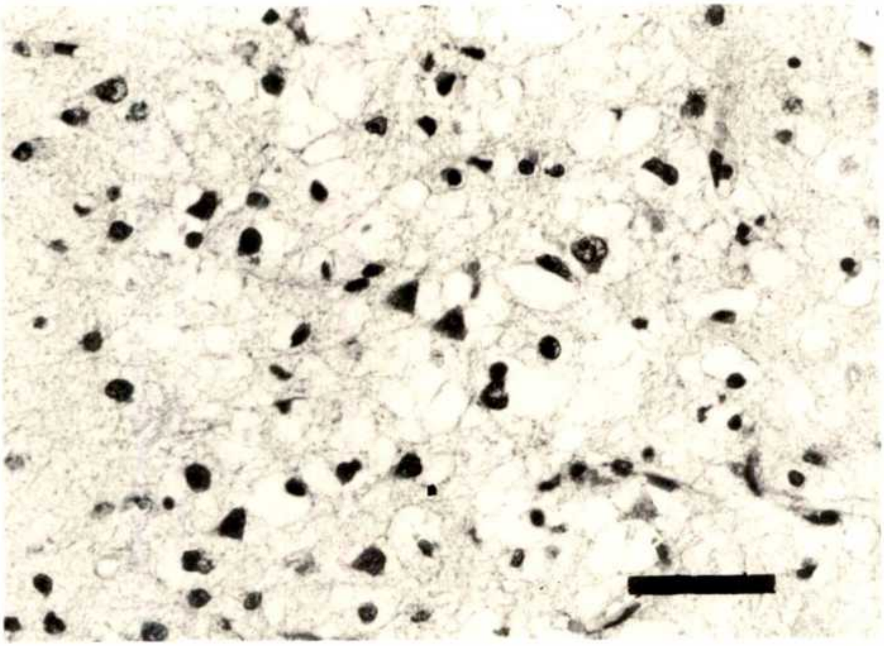

FIG. 9. *Case II-6*. Frontal cortex at higher magnification, showing status spongiosus in relation to nerve cells. Hæmatoxylin and eosin. Bar = 50 μm.

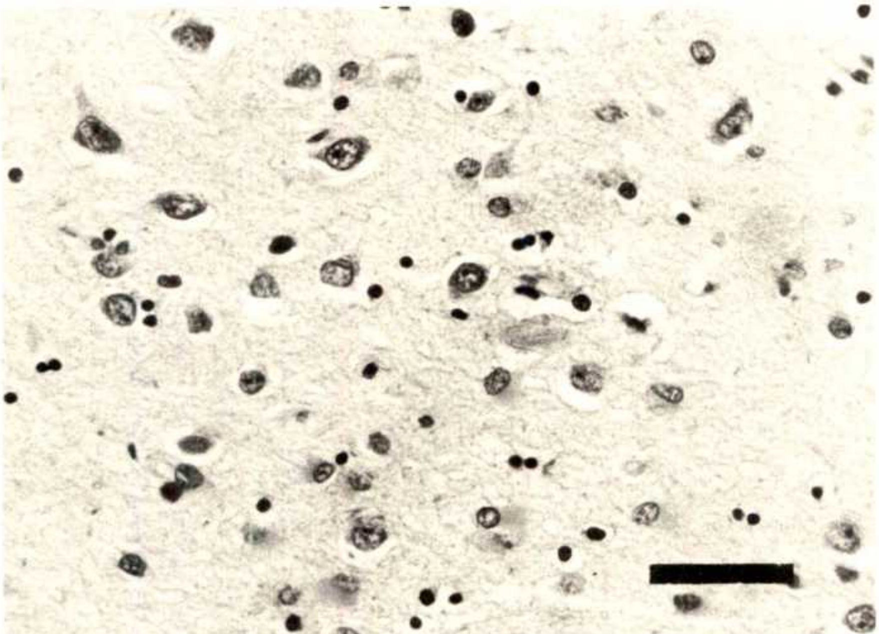

FIG. 10. *Case II-6*. Frontal cortex showing proliferation of hypertrophied astrocytes. Hæmatoxylin and eosin. Bar. = 50 μm.

Case II-9

Around the age of 46 years this man, an electrician by trade, was observed by his wife to be somewhat lethargic and withdrawn and 'just not himself.' Subsequently he became quite forgetful and seemed to sleep an inordinate amount. He was admitted to the hospital at the age of 48 years, at which time the neurological examination was normal except for tests of higher integrative function. His affect was flat. Although he knew who he was and where he was, his orientation for time was very poor. Serial 7s were performed within two minutes, with five mistakes. He could not remember specific events that had occurred a few minutes or a few years previously. He was able to repeat 7 digits forward and 4 backward, but he was unable to recall any of 3 unrelated words after two minutes had elapsed. Intellect was severely impaired. He seemed totally unaware of the nature or severity of his illness. Proverb analysis was concrete with poor interpretation.

Routine laboratory data, including blood count, serum chemistries, analysis of the cerebrospinal fluid and x-rays of the chest and skull, were normal. EEG showed questionable slowing in the left temporal region. PEG disclosed the presence of diffuse cerebral cortical atrophy with mild ventricular enlargement.

Upon re-evaluation nineteen months later (at the age of 50 years), he was judged to have deteriorated. He was completely disorientated as to time and place and was unable to perform any calculations. He was dysarthric but not aphasic, and he walked with a shuffling gait. The remainder of the neurological examination was normal. Cerebrospinal fluid analysis and brain scans were normal. PEG again showed widening of sulci, particularly frontally, and mild ventricular enlargement.

While living at home, he continued to deteriorate. He became doubly incontinent and was confined to a wheelchair. His family found it very difficult to communicate with him, either verbally or in writing.

At 51 years of age, he was committed to a state psychiatric institution. Up to this time he had received no medications. Examination on admission showed him to be apathetic and occasionally irritable. He responded poorly to verbal commands, but he followed moving objects with his eyes. A mask-like facial expression was noted. There was some rigidity in all four limbs, and he required assistance in dressing and undressing himself. Deep tendon reflexes were mildly hypoactive, and no Babinski responses were elicited. In hospital he received amitryptyline hydrochloride, 30 mg daily, chlorpromazine hydrochloride, 100 mg daily, and triflupromazine hydrochloride, 40 mg daily. His condition remained stable until his death from bronchopneumonia at the age of 52 years, approximately five years after the onset of neurological illness.

Autopsy was not performed.

DISCUSSION

Four of the ten siblings in the family described above have suffered a progressive dementing illness of approximately five to six years' duration. A fifth (II-2) may also have been affected, although we cannot be certain of this on the basis of the small amount of information that could be obtained regarding her illness. In those examined pathologically (II-1, II-5 and II-6) the findings were strikingly similar and consisted primarily of widespread cerebral atrophy (particularly frontally) with nerve cell loss, astrocytosis and, most notably in the outer cortical layers, microcystic rarefaction. Subcortical involvement was more variable but generally less intense except in the dorsomedial nucleus of the thalamus, which was severely affected in cases II-5 and II-6. Morphological alterations were also noted within Sommer's sector of the hippocampus in all three cases.

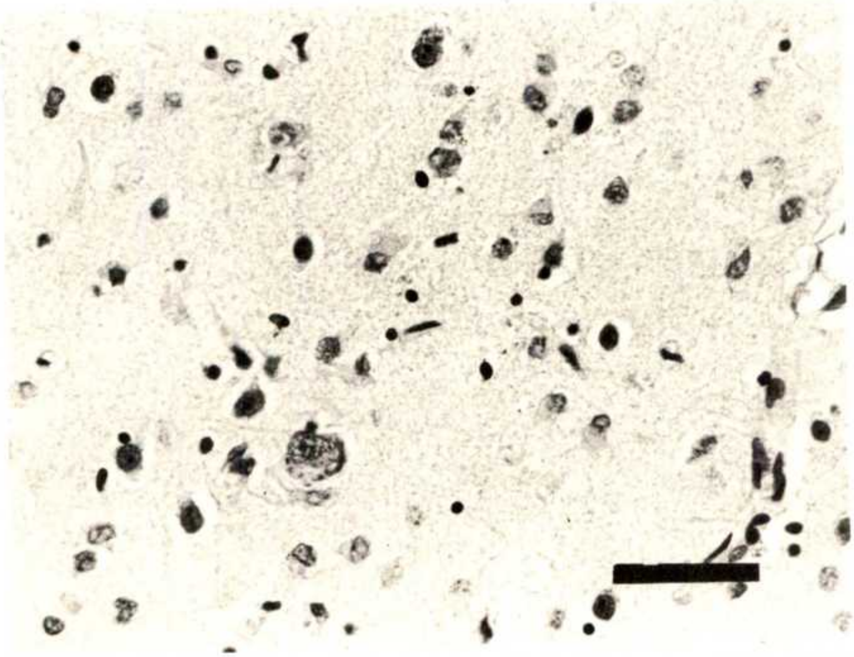

FIG. 11. *Case II-6*. Putamen showing nerve cell loss and astrocytosis. One large neuron is visible within this field. Hæmatoxylin and eosin. Bar = 50 μm.

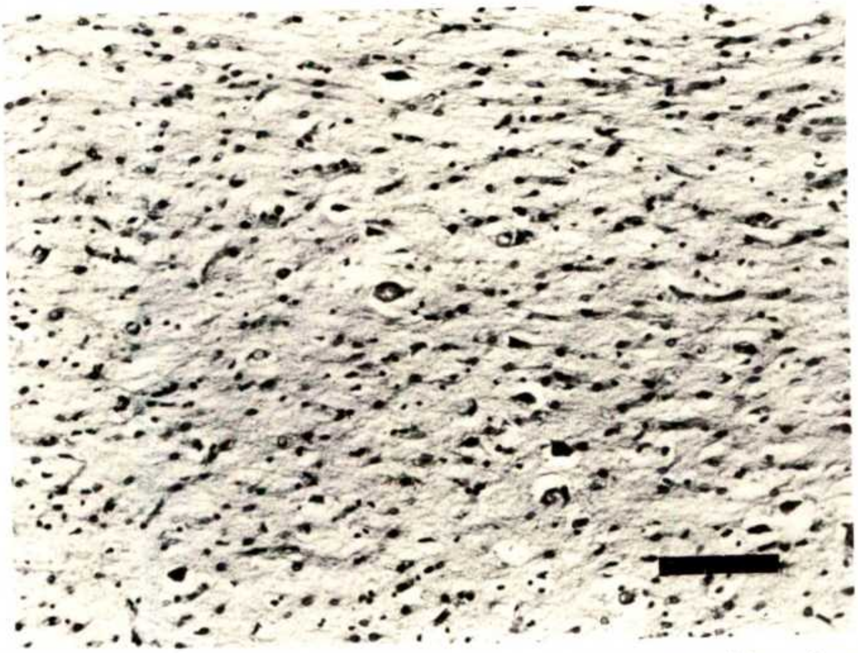

FIG. 12. *Case II-6*. Dorsomedial nucleus of the thalamus showing rarefaction, nerve cell loss and astrocytosis. Hæmatoxylin and eosin. Bar = 100 μm.

The variability of clinical presentation is worthy of comment. Early in the course of illness, loss of recent memory and temporal orientation, followed by impairment of abstractive and calculative ability, insight and judgement, were characteristic of all affected members, but belligerent hyperactivity was noted only in II-1, hyperphagia only in II-5 and lethargy and hypersomnia only in II-9. Affect was labile in II-1 and II-5 and flat in II-9. Urinary and fæcal incontinence appeared early in II-1 and later in the others. The development of rigidity of extrapyramidal type in II-1 and II-9 antedated the institution of therapy with psychotropic drugs, and was therefore clearly an intrinsic feature of the illness in those patients. All eventually developed abnormalities of gait as well as disordered speech and comprehension progressing to mutism.

Although the condition is clearly familial, it may not be hereditary, as we have not been able to document the presence of a similar illness in the parents or in any other branch of the family. Of particular interest is the finding that the onset of dementia in three of the siblings (II-1, II-5 and II-6) seems to have occurred over a six-month period, eight to nine years after the first (II-9) became ill.

Among the well-recognized forms of familial dementia of adult onset, Huntington's disease, Wilson's disease, and the familial forms of multi-infarct dementia, the senile dementia-Alzheimer disease complex and congophilic angiopathy can be eliminated from consideration in this family because of the absence of the characteristic clinical and/or neuropathological findings. The long duration of illness, the absence of myoclonus and the absence of specific EEG changes set this family's illness quite apart from Creutzfeldt-Jakob disease clinically (Masters *et al.*, 1979). Pathologically, although status spongiosus was seen, the spongiform change described by Masters and Richardson (1978) as being pathognomonic for Creutzfeldt-Jakob disease was not observed.

The possibility of Pick's disease is more difficult to rule out, largely because there appears to be some uncertainty in the literature regarding the pathological criteria needed to make such a diagnosis. Some investigators in the past appear to have relied upon the presence of grossly circumscribed cerebral atrophy as the principal means of making the diagnosis of Pick's disease (Sjögren, Sjögren and Lindgren, 1952; van Mansvelt, 1954; Tissot, Constantinidis and Richard, 1975). We feel that such an approach is misleading. Tariska (1970), for example, has described circumscribed atrophy in Alzheimer's disease. The gross photograph (Case 1, fig. 2) that appears in the report by Haltia, Kovanen, van Crevel, Bots and Stefanko (1979) shows severe focal atrophy of the temporal lobe in a case of Creutzfeldt-Jakob disease. Finally, in studying some of the cases compiled from the literature in van Mansvelt's (1954) treatise on Pick's disease, we have noted that many showed only senile plaque formation and neurofibrillary degeneration, findings that would now be regarded as typical of Alzheimer's disease. In our cases (II-1, II-5 and II-6) cerebral atrophy was not sharply circumscribed, although the pathological changes in the cerebral cortex were not uniformly intense, either grossly or microscopically.

We were not able, upon careful searching, to find either ballooned nerve cells or argyrophilic Pick inclusion bodies in any of our cases. It has been stated repeatedly that such findings are not present in all cases of Pick's disease (Jervis, 1971; Corsellis, 1976). Indeed, Schneider (1927) and von Braunmühl (1930) suggested that their appearance represented only a phase in the morphological progression of the disease. van Mansvelt (1954), however, in his detailed analysis of the literature, found that the occurrence of ballooned neurons or Pick bodies was not directly related to the duration of the illness. In our view, it remains to be proven that Pick bodies can disappear altogether from the cerebral cortex of a patient with Pick's disease. In the absence of the typical gross or microscopic features, therefore, we do not feel justified in classifying the condition affecting the family we have described under the heading of Pick's disease.

The clinical pattern of our cases differs from that of Pick's disease in several respects. Although there is disagreement as to whether or not Pick's disease can be differentiated clinically from other forms of dementia of late onset, particularly the senile dementia-Alzheimer disease complex, Pick's disease is said classically to be characterized by progressive dementia, with early social, ethical, and moral deterioration, loss of spontaneity and initiative (or, occasionally, restlessness with stereotyped reactions), relatively mildly disturbed speech, ideomotor apraxia and, in the later stages of illness, incontinence (Sjögren *et al.*, 1952; van Mansvelt, 1954; Wilson, 1954; Haase, 1977; Tissot *et al.*, 1975). Certain of the presenting clinical features of the patients we have described, *viz.*, incontinence (II-1), hyperphagia (II-5), and hypersomnolence (II-9), are not typical of Pick's disease. In addition, abnormalities of gait (noted in all affected members) and rigidity of extrapyramidal type (II-1 and II-9) are said to be far more characteristic of Alzheimer's disease than of Pick's disease (Sjögren *et al.*, 1952); it is thus not surprising that most of the affected members of this family carried the diagnosis of Alzheimer's disease during life.

Five of the reports referred to in van Mansvelt's review describe familial cases of dementia in which, although gross focal cerebral atrophy was evident at autopsy, no ballooned nerve cells or argentophilic Pick bodies were noted; nevertheless they were considered to be examples of Pick's disease (Grünthal, 1930; Haškovec, 1934; van der Heide, 1934; Bonfiglio, 1937; Mallison, 1947). On the basis of the descriptions provided, we are not able to determine with certainty whether or not all these cases belong within the same diagnostic category, or if any of them exemplify the same condition that our cases do.

Neumann and Cohn (1967) described a familial form of dementia of long duration characterized by severe nonfocal cerebral atrophy. Their cases bear some resemblance to ours, except that they judged the pathological alterations (mainly astrocytosis) to be much more intense in the white matter than in the cerebral cortex. In our material, the changes in the white matter, being less severe than those in the overlying cerebral cortex, were more likely secondary rather than primary.

Schaumburg and Suzuki (1968) reported their findings in a family, six members of which developed dementia during the third to fifth decades of life. In a critical review of the subject of Kraepelin's disease, to which they considered their cases bore a superficial resemblance, they concluded that the heterogeneous nature of the condition did not justify retention of the eponym. The material that formed the basis of their report was characterized by severe transcortical nerve cell loss, particularly in layer 6, with moderate gliosis of the molecular layer and the subcortical white matter. Our cases, by comparison, showed more intense involvement of the outer cortical layers. In addition, although they encountered occasional vacuolated nerve cells, status spongiosus of the degree noted in our cases was not described.

In conclusion, we have not been able to classify diagnostically to our satisfaction the dementing disorder which has afflicted the family we have described. Nor have we been able to find any cases in the literature with the same topographical distribution of lesions.

SUMMARY

A family is described in which 4 of 10 siblings developed a dementing illness that culminated in death within five to six years of onset. The pathological findings in 3 members were strikingly similar, and consisted of widespread nerve cell loss and astrocytosis within the cerebral cortex, status spongiosus within the outer cortical layers and, in 2, nerve cell loss and astrocytosis within the dorsomedial nucleus of the thalamus. It is concluded that the disorder described in this report does not conform precisely to any of the currently recognized categories of familial dementing disease.

ACKNOWLEDGEMENTS

The authors wish to thank Dr Colin Masters of the National Institutes of Health, Bethesda, Maryland, who has examined the slides and concurred with our observations and undertaken inoculation studies with our material. We also wish to thank Ms Elinor Carbone for fig. 1.

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(*Received April 22, 1980*)

Brain (1981), **104**, 79-95

DISTRIBUTION OF CEREBRAL LESIONS IN ACQUIRED HEPATOCEREBRAL DEGENERATION

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INTRODUCTION

THE work of Wilson (1912) focused attention on the relationship between cirrhosis and cyst-like softening of the basal ganglia. In the same year, Hösslin and Alzheimer described extensive unusual astroglial abnormalities in the condition then known as pseudosclerosis. During the next decade, it became apparent that Wilson's disease or hepatolenticular degeneration, and pseudosclerosis, were in fact the same; that Wilson had taken too narrow a view of the extent of the brain lesions, and placed undue emphasis on those in the lenticular nuclei; and that the cortical and subcortical abnormalities previously described by Homén (1892), and Anton (1908), were indeed manifestations of Wilson's disease (Spielmeyer, 1920). The astroglial alterations have become known as the Alzheimer type 1 and 2 abnormalities, while the process leading to a network of cavities filled with fluid or gelatinous material is usually called spongy change or spongy degeneration. Although neither alteration is specific, when found together they are the hallmark of hepatocerebral degeneration.

The first description of microscopic spongy change together with Alzheimer glia in non-Wilsonian, or acquired hepatocerebral degeneration, is that of van Woerkem (1914). The histological features of acquired hepatocerebral degeneration seem identical to those of Wilson's disease (Waggoner and Malamud, 1942; Adams, 1965), and although there is no large accumulation of copper in the former disorder, the other biochemical abnormalities can be similar (Warnock and Neill, 1958; Gibson, 1963). These observations would lead one to suspect that liver damage *per se* is the cardinal abnormality underlying hepatocerebral syndromes were it not that the alteration in hepatic architecture is sometimes much less than would be expected from the severity of the brain lesions (Schmincke, 1920; Wimmer, 1921; Eicke, 1941;

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Inose, 1952; Graham, Adams, Caird and Lawson, 1970). Conversely, neurological complications are not invariable in severe chronic liver disease.

In the 19th century, experiments in Pavlov's laboratory showed that a dog with Eck's fistula could develop the syndrome now called hepatic encephalopathy (Hahn, Massen, Nencki and Pavlov, 1893). Portal-systemic anastomoses performed for the relief of portal hypertension in cirrhotic patients may precipitate cerebral complications, and there have been occasions when portal-systemic shunts have led to hepatocerebral degeneration in the absence of primary liver disease (McDermott and Adams, 1954; Baltzan, Olzewski and Zervas, 1957). It seems, then, that the one feature common to these hepatocerebral syndromes is that portal blood can reach the brain without first being acted on by the liver. Portal blood that has bypassed the liver apparently contaminates the systemic circulation with substances toxic to the brain, and over a long period of time may cause irreversible brain lesions. Certain parts of the brain are especially likely to be damaged, and this suggests that there are regional differences in cerebral vulnerability to this type of injury. Portocaval shunting in the absence of primary liver disease is relatively uncommon, and we have therefore taken the opportunity to further document the cerebral complications of this condition in two patients, and to compare the findings with those of a cirrhotic patient, with particular attention being given to the question of selective vulnerability.

CASE REPORTS

Case 1

This housewife with portal hypertension secondary to periportal fibrosis underwent splenorenal venous anastomosis at the age of 61 years, and developed signs of cerebral dysfunction nine years later. At the outset, there were only grimace-like involuntary facial movements, slight difficulty with abstract thought and a shortened attention span; but the symptoms gradually increased in severity until death at the age of 75 years. The clinical deficits fluctuated in severity, but during the last year of life she was at all times confused, apathetic, and incapable of self care. Speech was slow and poorly articulated, and the voice was faint and expressionless. The eyes were often held tightly closed, and at the same time the corners of the mouth were retracted in a dystonic grimace. There was frequent smacking of the lips, protrusion of the tongue, and slow side-to-side movements of the tongue within the mouth. Limb movements were interrupted by lapses of postural control, and slight to moderate coarse tremor appeared when precise movements were attempted. Occasional small, jerky, choreiform movements were noted in the face and upper limbs, and slight rigidity could be detected on passive movement of the limbs. The tendon reflexes and plantar responses were normal. There was stupor, increased rigidity, and hypotension in association with gastrointestinal hæmorrhage during the last three weeks of life.

Routine hæmatological and biochemical investigations were normal except that the serum alkaline phosphatase was 25 King Armstrong units. Other routinely tested parameters of liver function such as serum bilirubin and transaminases, and the prothrombin time, were always normal. The serum ceruloplasmin was 250 units (normal greater than 100).

Case 2

This retired medical orderly had a disorder of the nervous system which began at the age of 65 years and gradually progressed in severity until he died of bronchopneumonia at the age of 72 years. There was no familial illness, and the main past illness was stricture of the common bile duct secondary to choledocholithiasis at the age of 59 years. Normal biliary drainage was restored over a period of eighteen months by T-tube insertion and repeated mechanical dilation of the stricture. The serum bilirubin and alkaline phosphatase levels returned to normal, and there was no further evidence of hepatobiliary dysfunction.

An EEG, done after two episodes of transient loss of consciousness at the age of 65 years, showed diffuse slowing with activity as slow as 3 Hz, but no evidence of focal abnormality. Although there was no asterixis or mental impairment, repetitive movements of hands and feet were slow and arrhythmic. There was no alteration of consciousness in the next three years except for a brief period of confusion during an acute bladder infection. During the last two years of life he was weak and debilitated, and could not walk without support. He showed no interest in his environment and would sit with open mouth and vacant stare, and when disturbed would sometimes cry out in a confused manner. There were a few episodes of light stupor during the acute phase of respiratory infections. Slow, rolling involuntary movements of the tongue became prominent; the speech was slow, and the voice poorly modulated, sounding like a recording played at half the normal speed. In the last six months of life there were slow athetoid movements of the upper limbs, and also occasional fleeting choreiform movements. All involuntary movements were augmented by activity and disappeared during sleep.

Case 3

This salesman died suddenly at the age of 58 years because of aspiration of blood during hæmatemesis. He was an alcoholic, and known to have cirrhosis and œsophageal varices for at least six years, but had no evidence of any cerebral disorder until about six months before death, when he was brought to hospital in hepatic stupor. With vigorous medical therapy he became alert but remained confused, and would roll his head from side-to-side in a restless manner, while the tongue moved slowly about the mouth, and the face passed through a series of grimaces. Action tremor interfered with the more deliberate voluntary movements, but asterixis was only occasionally demonstrable. The voice was indistinct and monotonous, and seemed to be produced with great effort. During the last three months of life there were shock-like choreiform movements of the face and hands, and slow, athetoid movements of the upper limbs and body. These choreo-athetotic movements were not present during periods of complete rest. The tendon reflexes were slightly brisker than normal, but the plantar responses remained flexor. There was no abnormal corneal pigmentation. The serum ammonia level was 150 μg/100 ml three weeks before death, and the EEG showed diffuse 3 to 4 Hz slow activity. Routine laboratory investigations of the blood, urine and spinal fluid were normal.

AUTOPSY FINDINGS

General Examination

Case 1 died of hæmorrhage from a duodenal ulcer, and Case 3 of hæmorrhage from œsophageal varices. The livers were small, the weights being 640, 770, and 1100 g for Cases 1, 2 and 3, respectively. The splenorenal venous anastomosis of Case 1 was patent. In Case 2, the midportion of the portal vein was occluded by inspissated thrombus and fibrous tissue, and there was extensive scarring in surrounding tissues. On microscopic examination, slight periportal fibrosis was found in Case 2; in Case 1, there was moderately severe periportal fibrosis, and slight fatty change; and in Case 3, micronodular cirrhosis.

Brain weights were: Case 1, 1040 g; Case 2, 1225 g; and Case 3, 1200 g. There was only slight to moderate atherosclerotic involvement of major cerebral arteries. A slight degree of senile atrophy was noted in the temporal lobes of Case 1. There was a small infarct in the left putamen of Case 3, and a small focus of myelinolysis in the central pons of Case 2; both lesions appeared to be of long duration.

Hepatocerebral Lesions

Grey, translucent areas were seen in the frontoparietal cerebral cortex, and in the lenticular nuclei of all cases (fig. 1). The cortical lesions were in the posterior ends of F1 and F2, and the upper portions of the precentral gyri and parietal lobes (figs. 1 and 2). In the frontal lobes, the area of most severe involvement centred on F2 (fig. 2), and tended to be slightly closer to the midline in the parietal lobes. When these lesions were followed through consecutive coronal sections, their transverse extent varied, being greatest in the parietal lobe where there was some extension to

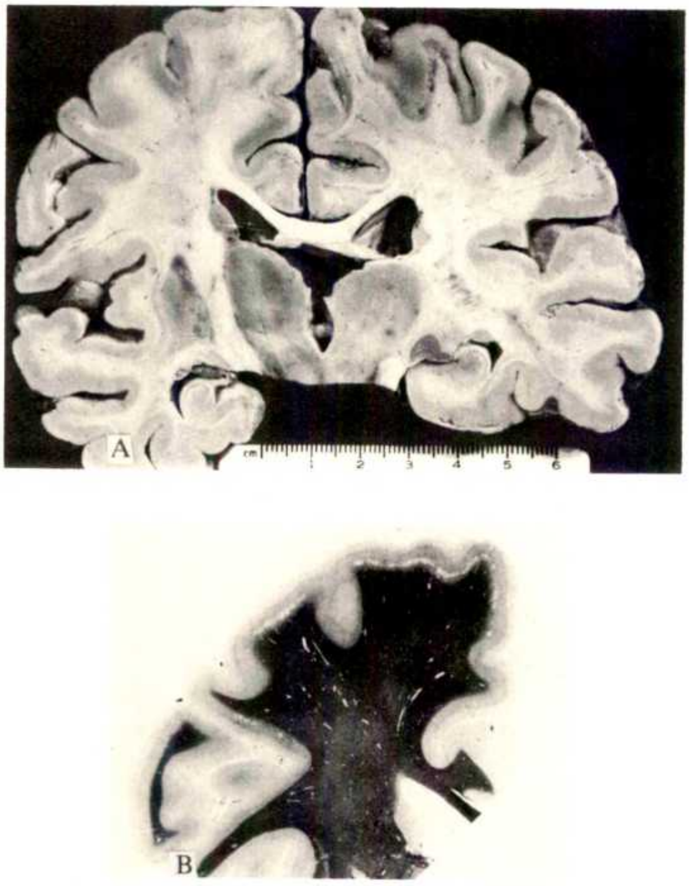

FIG. 1. *Case 1.* A, coronal section through the frontoparietal junction shows spongy degeneration in the upper cerebral convexities, mainly in crowns of gyri; and in the lenticular nucleus, mainly in the upper pole of the putamen. The cortical lesions in the left hemisphere are not well seen but are apparent in B, a myelin-stained section taken from the left half of the brain slice shown in A.

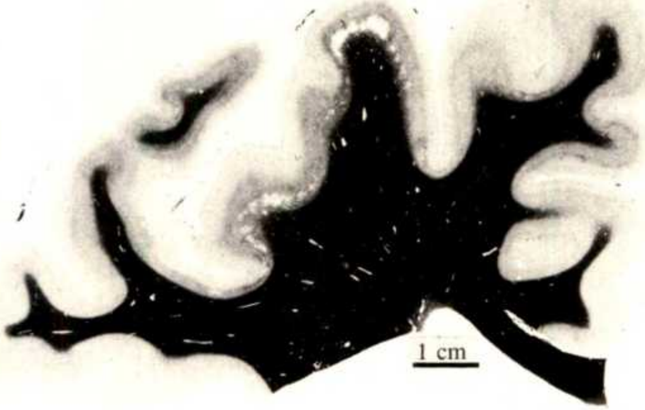

FIG. 2. *Case 3.* Posterior frontal coronal section, showing the cortical lesions to be mainly in the crown of F2. Myelin stain.

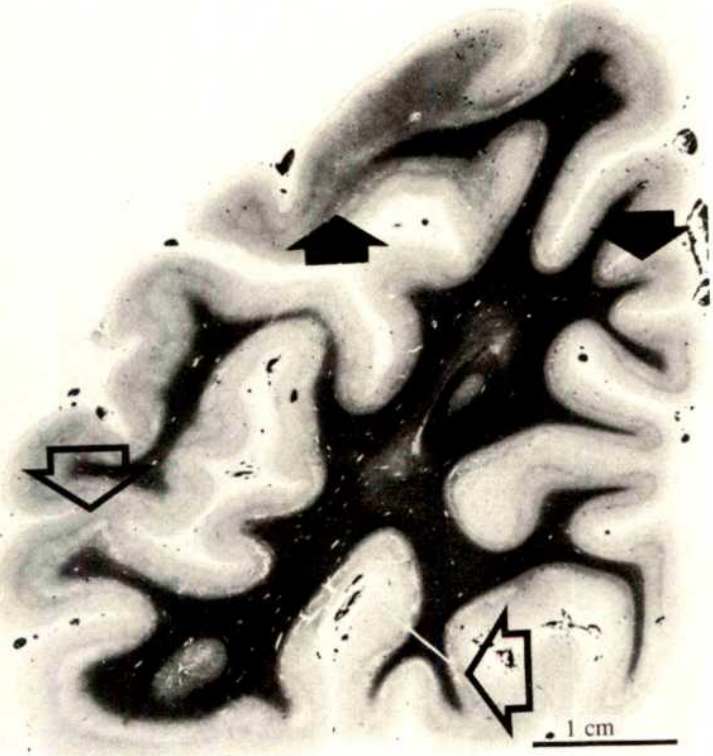

FIG. 3. *Case 1.* Myelin-stained coronal section of occipital lobe. Cortical spongy change is mainly in crowns of gyri between the open arrows, and greatest in extent at the inferolateral angle of the hemisphere. Recent ischæmic damage is superimposed on smaller lesions in depths of sulci. Solid arrows indicate areas where microcavitation was seen at higher magnification. Note sparing of central territories of major arteries.

the upper, medial face of the hemisphere. The depths of sulci were affected, but the crowns of gyri were more constantly and more severely involved. In the lenticular nuclei, the abnormality was greatest in the upper part of the putamen, and there was some extension to the adjacent internal capsules and caudate nuclei.

On microscopic examination, the translucent lesions were found to be the result of sponge-like transformation of the grey matter by myriads of tiny fluid-filled cavities. Additional areas of microcavitation could be seen, those in the cortex being almost confined to the posterior frontal convexities and the parietal and occipital lobes. In the occipital lobes, the territory at the inferolateral angle of the hemispheres, between the regions supplied by the middle and posterior cerebral arteries, was consistently affected (fig. 3). The striate cortex was spared, but there was usually some spongy change higher on the medial aspect of the occipital lobe, and also in the upper hemispheric convexity.

The cortical spongy change seemed to begin as isolated vacuoles scattered anywhere between layer 5, and the deeper part of layer 3. Many of these vacuoles were near capillaries, but some appeared to be at a distance from vessels. In more severely involved areas blood vessel endothelium seemed to be thickened and to have an increased number of nuclei. The more extensive spongy lesions took the form of a band-like zone in the area normally occupied by cortical layer 4, sometimes reaching the subcortical white matter, but usually parts of layers 5 and 6 remained intact below this zone (fig. 4). There was loss of myelin and neurons in

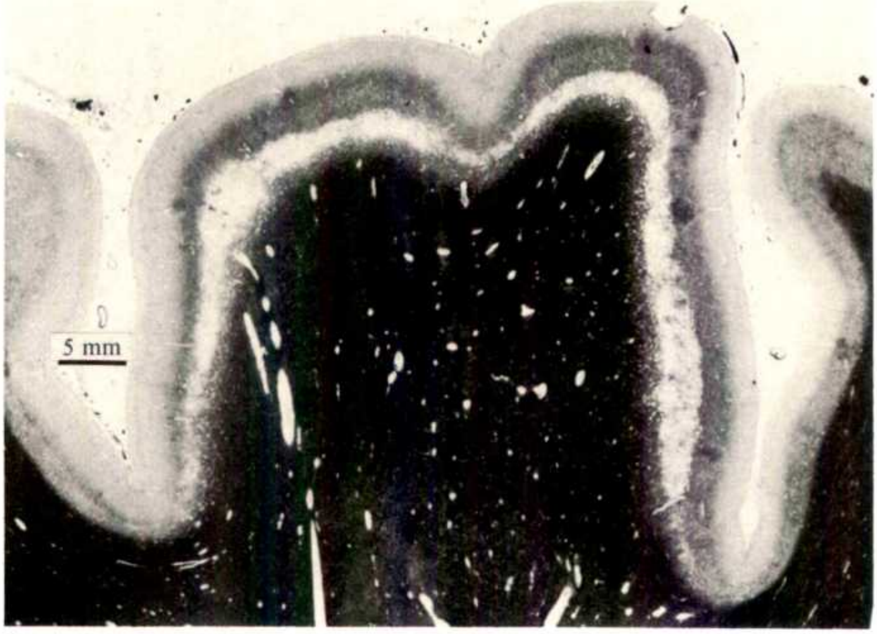

FIG. 4. *Case 2*. Myelin-stained section from the upper cerebral convexity. The spongy band appears to split cortical layer 4, leaving vacuolated remnants of layers 5 and 6 between the main lesion and the subcortical white matter.

these larger lesions, but only a few gitter cells were seen. This, along with the finding of occasional well preserved neurons surrounded by spongy cavitation, suggested a slowly progressive process leading to expansion of the cortex by the accumulation of fluid.

Case 1 differed in that there was an additional form of cortical damage that could be superimposed on the spongy degeneration, but was also found in isolation, especially in depths of sulci and in the areas between the posterior and middle cerebral arterial supply in the temporal lobes. In involved areas, there was neuronal loss and some degree of reactive change in astrocytes. Surviving neurons were shrunken, with pyknotic nuclei, and slightly eosinophilic cytoplasm. These abnormalities had the appearance of damage caused by ischæmia or hypoglycæmia, and since the Purkinje cells and hippocampal pyramidal cells were relatively spared, the former ætiology seems more likely.

In all cases, microcavitation was found in the pallidum, heads of caudate and putamen, subthalamus, ansa lenticularis and adjacent internal capsule, and in the cerebellar white matter near the dentate nuclei. A few vacuoles were also often seen in the thalamus. The microcavitation seemed to have a tendency to extend along the bundles of myelinated fibres in the globus pallidus and corpus striatum. There was sometimes some pallor of myelin staining in the lesions, but the spongy degeneration was never very extensive in the white matter.

Most astrocyte nuclei were enlarged, especially those in the grey matter, where there was florid Alzheimer type 2 change. Astroglia in the basal ganglia and in the deeper layers of the cerebral cortex were particularly affected, and many contained intranuclear inclusions with the staining reactions of glycogen. The involvement of the thalamus and upper brain-stem was of moderate severity, the least affected regions being the hippocampi and adjacent temporal lobes, and the cerebellar granular layer. A small number of Alzheimer type 1 astrocytes were found near the cortical spongy lesions of Cases 1 and 2 (fig. 5A). Many astrocyte nuclei directly within the spongy lesions were hyperchromatic (fig. 5B), and although more accurate assessment of DNA content would be necessary for certain identification, the small size of these nuclei at least served to discriminate them from classical Alzheimer type 1 glia.

DISCUSSION

Hepatoportal Abnormalities

Although the primary causes of their hepatoportal disorders differed, the patients developed remarkably similar clinical syndromes and brain lesions. Case 3 is an example of the common type of hepatocerebral disorder, in which parenchymal damage leads to cirrhosis, portal hypertension, and the development of portal-systemic shunts. There was minimal liver damage in Case 1, the major abnormality being periportal granulomatous inflammation and subsequent fibrosis. Although the nature of the interference with portal flow is uncertain in these circumstances, the site of blockage is probably intrahepatic (Mikkelsen, Edmondson, Peters, Redeker and Reynolds, 1965). Patients with this type of hepatic disorder have a relatively good chance of ten-year survival after portal decompression (Zeegen, Stansfeld, Dawson and Hunt, 1970), but many of the survivors eventually develop cerebral complications. Case 2 had longstanding portal vein thrombosis, and presents an example of hepatocerebral degeneration secondary to portal-systemic shunting because of intrahepatic portal obstruction without primary liver injury. A patient with similar findings was reported by Baltzan *et al.* (1957). Such cases are unusual in that portal vein occlusion tends to be a complication of liver disease, rather than a primary event, and they offer a rare opportunity to compare the effect of naturally developing portal-systemic shunts with surgical portocaval anastomoses, in the absence of parenchymal liver damage. Case 1 is an example of the latter situation, and clinical and autopsy details of two further patients were reported by Victor, Adams and Cole (1965). The clinical findings and cerebral lesions in all these patients were much the same as those occurring in association with chronic primary hepatic disease.

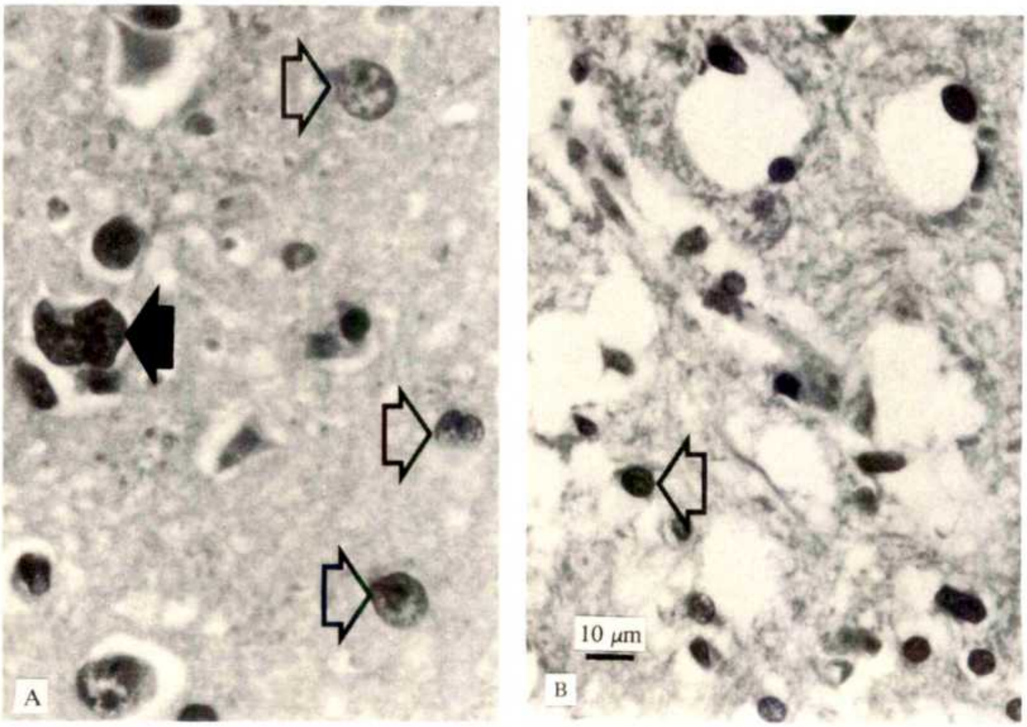

FIG. 5. *Case 2.* A, solid arrow indicates Alzheimer type 1 astrocyte, and open arrows Alzheimer type 2 astrocyte nuclei with intranuclear glycogen inclusions. B, arrow indicates one of many hyperchromatic astrocyte nuclei in cortical spongy lesion. Note that these nuclei are smaller than the typical Alzheimer glia shown with the same degree of magnification in A. Hæmatoxylin and eosin.

Despite the absence of ongoing hepatic disease, the livers of Cases 1 and 2 were small, as is usual in patients with portal-systemic shunts. While this atrophy leads to some change in hepatic function, it is likely that the alteration is more in hepatic storage capacity than in the ability of the liver to detoxify the portal blood (Thompson, Williams and Sherlock, 1964). Changes in the electroencephalogram (Read, McCarthy, Ajdukiewicz and Brown, 1968), and in cerebral blood flow (Bianchi Porro, Maiolo and Della Porta, 1969) occur too soon after surgical portocaval anastomosis to be accounted for on the basis of hepatic atrophy. It therefore seems that portal-systemic venous shunting is the one common factor in hepatocerebral degeneration, and that the major cause of the cerebral lesions is portal venous blood reaching the brain without prior modification by the liver.

Spongy Degeneration

The spongy lesions vary in location in Wilson's disease, and also in hepatocerebral degeneration associated with various other disorders of the liver or the portal vein, and there is nothing to suggest any pattern of cerebral involvement unique to one or other of these conditions. This variability also makes it difficult to distinguish a general pattern, but there certainly are some recurrent features that can be said to be characteristic of this group of diseases. Wilson (1912) found that in his cases the basal ganglia lesions were to some degree symmetrical, with the outer portions of the lenticular nuclei bearing the brunt of the damage. If the cavitation is not too extensive it can often be seen that the spongy change is most severe in the upper, lateral, lenticular nucleus, and this is also true of non-Wilsonian hepatocerebral degeneration (Waggoner and Malamud, 1942; Leigh and Card, 1949; Guillain, Bertrand and Godet-Guillain, 1954; Zieve, Mendelson and Goepfert, 1960; Victor *et al.*, 1965; Toghill, Johnston and Smith, 1967). When microcavitation is taken into account, both Wilsonian and acquired lenticular degeneration are usually accompanied by cortical lesions, but the association is not invariable (Graham *et al.*, 1970). With regard to the cerebral cortical spongy lesions: in Wilson's disease with severe involvement, an example being the patient of Anton (1908), the cavitation in the frontal lobe can be so extensive that it is difficult to postulate a pattern other than to say that such gross lesions seem to begin in the upper halves of the hemispheres. However, in many reports it is possible to tell from the descriptions and illustrations, that the major lesions were in the upper frontal convexities (Schütte, 1913; Schob, 1925; Barnes and Hurst, 1926; Braunmühl, 1930; Bielschowsky and Hallervorden, 1931; Konovalov, 1941). The gyri F1 and F2 tend to be severely involved, and Konovalov noted that the posterior ends of these gyri and the upper parietal convexities are particularily affected, the spongy degeneration arising mainly in the third to fifth cortical layers. In some cases the lesions have been especially severe in the posterior parts of the hemispheres (Spielmeyer, 1920; Jakab and Kõrnyey, 1948). The cortical spongy change has much the same distribution in other types of hepatocerebral degeneration, usually being most severe in the upper parietal and posterior frontal convexities (Leigh and Card, 1949; Guillain *et al.*, 1954; Baltzan *et al.*, 1957; Gibson, 1963; Victor *et al.*, 1965). Both the crowns of gyri and depths of sulci are affected in Wilson's disease and acquired hepatocerebral disorders, but as in our cases, the lesions are usually more extensive in the crowns of gyri. Almost symmetrical involvement of the latter was noted by Konovalov (1941), and in many other reports a similar pattern is either described or shown in the illustrations.

In many of the reports cited, the pattern of the cerebral lesions is not given in detail, but on the whole, the location of the major grey matter damage seems similar to that of our patients. There is sometimes mention of white matter damage, or as in our Case 1, neuronal loss in areas not affected by spongy degeneration. Such lesions are not always found, and it is not certain whether they are part of the hepatocerebral syndrome, or are caused by incidental factors such as anoxia or metabolic derangement that often complicate this form of illness. Nutritional disorders seem to be especially frequently associated with the extensive pseudoulegyric form of grey matter damage in hepatocerebral disorders which have been seen in Japan (Shiraki and Oda, 1968; Koga, Shimono, Tateishi and Ikuta, 1978). There has been speculation regarding a demyelinating form of Wilson's disease, but if such a condition exists, it is evidently a rarity (Miyakawa and Murayama, 1976). There are many reports where it appears that extensive grey matter lesions have merely extended to contiguous white matter (Barnes and Hurst, 1926; Bielschowsky and Hallervorden, 1931; Eicke, 1941; Schulman and Barbeau, 1963; Ishino, Mii, Hayashi, Saito and Otsuki, 1972). Other demyelinating lesions could be cerebral or pontine myelinolysis occurring as a non-specific effect of a variety of systemic metabolic disorders (Finlayson, Snider, Oliva and Gault, 1973); the pontine myelinolysis found in our Case 2 is presumed to be on this basis.

It is evident that the spongy lesions, a characteristic feature of all types of hepatocerebral degeneration, are especially likely to be found in the superolateral lenticular nucleus and adjacent caudate, and the upper parietal and posterior frontal convexities. The cortical lesions, in fact tend to be most extensive in the frontal, parietal and occipital regions that are borderland territories between the supply of major cerebral arteries, and therefore regions most vulnerable to hypoperfusion. According to Lindenberg (1963), circulatory stagnation is most likely to occur in the cortex of the upper parietal convexity during hypoperfusion, with the adjacent frontal and occipital grey matter being the next regions liable to damage; while the borderland areas in the temporal lobes are the least vulnerable. In our patients, where the spongy degeneration was of only moderate severity, the damage was almost confined to the more vulnerable areas. Borderland lesions may vary in position because of variation in the vascular anatomy (Meyer, 1953), so that asymmetrical lesions can be accounted for on this basis. The distribution of the brain lesions in rats with chronic portocaval shunts is also compatible with circulatory predisposing factors. Here, the vacuolation is largely confined to the depths of sulci in the cerebellar cortex, while the cerebral hemispheres, where there is little sulcal infolding, are spared (Cavanagh, Lewis, Blakemore and Kyu, 1972). In general, ischæmic damage is apt to be more severe in the depths of sulci, but lesions secondary to hypoperfusion can have the same crown of gyri distribution as that found in hepatocerebral degeneration in man (Brierley, 1976). Although the borderland concept is not entirely applicable to the circulation in the basal ganglia, the putamen and adjacent caudate are known to be especially vulnerable to hypoperfusion (Lindenberg, 1963; Brierley, 1976).

In view of the higher metabolic activity and blood flow in the grey matter, one might expect that a toxic abnormality of the arterial blood could be more damaging there. The greater vulnerability of grey matter in borderland arterial territories in hepatocerebral disorders suggests either a peculiarity of the circulation, or some type of acquired vascular damage in these areas. Schütte (1913), Spielmeyer (1920) and many others have stressed the importance of cerebral vascular proliferative changes in hepatocerebral degeneration, but it is difficult to be sure that these are in any way different from the usual vascular reaction to tissue injury. The transient decreases in cerebral perfusion pressure that occur during the normal course of events are perhaps great enough in the major borderland regions to render the affected grey matter more vulnerable to the stress presented by the shunted portal blood. Further stress could stem from the cutaneous and pulmonary vasodilatation and arteriovenous shunts, and changes in arterial oxygen saturation which may accompany cirrhosis (Berthelot, Walker, Sherlock and Reid, 1966). If these vascular phenomena also occur in the terminal arterial network of the brain, the metabolic derangement would probably be greatest in areas of borderland circulation, where there is more tendency to stagnation with drop in perfusion pressure.

Astrocyte Abnormalities

The Alzheimer type 2 astroglial changes were so extensive in the grey matter that it was difficult to determine any pattern of severity other than to say that the largest and most deformed astrocyte nuclei were found in the basal ganglia, deeper layers of the cerebral cortex, and the subthalamus; a distribution similar to that given by Hösslin and Alzheimer (1912) in the original description of this type of astroglial reaction. Their patient, who suffered from hepatolenticular degeneration without the cavitary lesions noted by Wilson (1912), also had severe involvement of the dentate nucleus. Alzheimer was impressed by the hyperchromatic appearance of many of the enlarged astrocyte nuclei. This variant, now known as the type 1 astrocyte, has about double the nuclear DNA content of the type 2 cells (Lapham, 1962). The type 1 astrocyte, believed to acquire an abnormal chromatin content because of aberrant cell division, appears among the reactive glia at sites of physical injury in brains of animals with portocaval anastomoses (Cavanagh and Kyu, 1971). In our material the Alzheimer type 2 change was severe in the grey matter adjacent to spongy degeneration, and less severe directly within the spongy lesion. Astrocyte nuclei in the latter situation were often hyperchromatic, but were smaller than those typical of type 1 cells. Presumably, such astrocytes represent a mixed reaction pattern, on the one hand to the metabolic stress of portal-systemic shunting, and on the other to tissue injury by the spongy change.

It seems likely that the type 2 astrocyte and the spongy degeneration, are manifestations of the same pathological process. Both abnormalities are found predominantly in the grey matter, and where a pattern of severity of type 2 astrocytic change can be determined, the distribution approximates that of the spongy lesion. The latter lesion, like the astrocyte change, can be linked to the metabolic effect of blood bypassing the liver to reach the blood-brain barrier. In rats, removal of the liver from the circulation leads to abnormalities in the transport of substances between the blood and the brain, and to increased pinocytosis with accumulation of fluid in astrocytes and the extracellular space (Livingstone, Potvin, Goresky, Finlayson and Hinchey, 1977; Finlayson, Potvin, Hinchey and Goresky, 1978). This movement of fluid into astrocytes is also a feature of the cerebral complications of cirrhosis (Martinez, 1968), and of animals with portocaval anastomoses (Norenberg, Lapham, Benson and May, 1972; Zamora, Cavanagh and Kyu, 1973). There is evidence that the formation of the type 2 astrocyte is a progressive event leading to hydropic degeneration (Zamora *et al.*, 1973; Norenberg, 1977), and it is likely that the spongy lesions represent the effect of this process combined with the further influence of circulatory factors.

Clinical Syndrome

Lapses of postural control (asterixis) and stupor, although typical manifestations of the hepatocerebral syndrome (Strümpell, 1898), can be intermittent and are not likely to be primary effects of the degenerative (fixed) cerebral lesions. Most of the stable clinical deficits can be classified either as dementia or as disorders of movement. In our patients, these symptoms were of insidious onset, and although there was fluctuation in severity they were gradually progressive without remission, and therefore are thought to be at least in some degree the result of the spongy degeneration.

The mental changes took the form of a global dementia without focal signs, such as dysphasia or agnosia. The dementia was not severe until late in the course of the illness, and at that point was not easily evaluated because the patients were apathetic and unreactive, with short attention span, and lack of interest in their environment. Signs of focal parietal lobe disturbance, as are said to occur with ischæmic cerebrovascular borderland lesions (Romanul, 1970), if present, were not detected. Victor *et al.* (1965), in their large series of patients with acquired hepatocerebral degeneration, also noted lack of correlation between the parietal lesions and the clinical deficits. Visual disorders that could have been on the basis of agnosia have been seen with pseudosclerosis (Hösslin and Alzheimer, 1912), and it has been noted that dogs with chronic portocaval shunts may behave as if blind (Hahn *et al.*, 1893). Occasionally, in hepatocerebral syndromes there are also signs suggestive of focal frontal lobe damage such as tonic lateral deviation of the eyes (Anton, 1908), grasp reflexes (Richter, 1948); and the personality changes also have some of the features of a frontal lobe disorder.

Asterixis is a variable manifestation of this disease, and therefore is not always part of the motor disorder, but if present, these lapses of postural control may adulterate other movement disorders and complicate their assessment. In our patients, intention tremor, and coarseness and irregularity of repetitive movements, could be seen when asterixis was not demonstrable. Clinical manifestations of this type are almost the rule in chronic hepatocerebral syndromes, and are often attributed to cerebellar dysfunction (Herz and Drew, 1950; Victor *et al.*, 1965). We did not find serious morphological alteration of the cerebellum, and suspect that the tremor and inco-ordination have a complex ætiology, and are probably the result of involvement of structures receiving cerebellar connections in the brain-stem or at a higher level. Certainly the dysarthria was not typical of cerebellar speech defects, but was more dystonic in character, as might be seen in diseases affecting the basal ganglia. Rigidity, and some degree of restless semipurposive movements were noted later in the illness, and eventually there was athetoid posturing of the limbs. The over-all clinical picture can resemble Huntington's chorea (Victor *et al.*, 1965), and it is of interest that in both conditions the lesions are liable to be especially severe in the putamen. Our patients all developed a curious facial appearance, with a staring expression, open mouth, grimace-like retraction of the lips, and restless involuntary movements of the tongue; that seems characteristic of hepatocerebral degeneration. There is repeated mention of this facies in even the earliest reports of this type of illness (Ormerod, 1890; Homén, 1892; Wilson, 1912), and one must suspect that this clinical finding is a reflection of the pattern of lesions in the basal ganglia. However, the fact that all our patients had much the same lesions and clinical findings is contrary to the experience of Victor *et al.* (1965), who found some difficulty in correlating the fixed lesions with their clinical manifestations. This probably means that there is a stage when the degenerative process has not progressed to irreversible alteration of morphology, but is none the less symptomatic.

SUMMARY

The brain lesions of our patients with chronic portal-systemic venous shunts were much the same regardless of the presence or absence of primary liver disease. Alzheimer's type 2 abnormality of astrocytes and demarcated areas of spongy degeneration were found, mainly in the grey matter, with more severe involvement of the basal ganglia and the deeper layers of the frontal, parietal and occipital cortex. The spongy degeneration showed an especially close correlation with the arterial blood supply, being greatest in borderland areas that fall between the regions usually supplied by one or other of the major cerebral arteries. Previous investigations have not been primarily concerned with selective vulnerability so that comparisons are difficult, but on review, there is evidence that this pattern of involvement is a feature of both Wilson's disease and acquired hepatocerebral

degeneration. The toxic effect of the portal blood is greatest in the grey matter, probably because of the greater metabolic activity there, and the distribution of lesions within this area of greater vulnerability appears to be further influenced by circulatory factors.

ACKNOWLEDGEMENTS

Celine Lemay provided technical help and prepared the illustrations, and the Department of Veterans' Affairs gave generous financial support. We are especially grateful to Dr Alex Aronoff, Chief of Medicine at Sainte Anne's Hospital, for asking us to see Case 3 and many similar patients, and for his advice and encouragement.

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(Received May 6, 1980)

Brain (1981), **104**, 97–116

DELAYED AND ENHANCED LONG LATENCY REFLEXES AS THE POSSIBLE CAUSE OF POSTURAL TREMOR IN LATE CEREBELLAR ATROPHY

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INTRODUCTION

WHEN standing upright, patients with late cortical cerebellar atrophy (atrophie cérébelleuse tardive à prédominance corticale, Marie, Foix and Alajouanine, 1922) show a characteristic and reproducible anteroposterior postural tremor at 3 Hz. Silfverskjöld (1969, 1977*a*, *b*), Dichgans, Mauritz, Allum and Brandt (1976) and Mauritz, Dichgans and Hufschmidt (1979). The predominant cause is a selective atrophy of Purkinje cells restricted primarily to the vermis and paravermis of the anterior lobe to which the proprioceptive afferents project (Victor, Adams and Mancall 1959). This syndrome may therefore serve as a model for studies of paleocerebellar function in the stabilization of human stance.

Recent work indicates that stability of upright posture on firm ground does not depend mainly on the integrity of spinal stretch reflexes (Gurfinkel, Lipshits and Popov, 1974, Gurfinkel, Lipshits, Mori and Popov, 1976; Nashner, 1976; Burke and Eklund, 1977) but involves phylogenetically younger, more powerful and adaptable long-loop reflexes running through higher centres such as the motor cortex and presumably the cerebellum (Phillips, 1969; Melvill-Jones and Watt, 1971; Evarts and Tanji, 1976).

Murphy *et al.* (1975*a*, *b*), in thinking about a physiological basis for cerebellar dysmetria and tremor in arm movements, postulated and later confirmed that those areas of the cerebellum which receive afferent projections from the periphery (that is, the paleocerebellum for proprioception) are parts of a feedback loop for position control. Oscillation in such a feedback system can occur if the gain is too high or the loop-time is too long (Stein and Oguztöreli, 1976; Murphy *et al.*, 1975a).

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Encouraged by preliminary results which had demonstrated underdamped rhythmical discharges of the anterior tibial muscle after a single electrical stimulus to the tibial nerve (Mauritz, Dichgans and Schmitt, 1978) we tested this concept of a long-loop instability in our patients with postural tremor due to anterior lobe lesions. Evaluation of results obtained from patients required rather extensive studies of normals, the results of which are also presented.

METHODS

Biomechanical recordings of posture were obtained by a force measuring platform, a hip and head goniometer and an ankle angle measuring device, sufficiently described in preceding papers (Dichgans *et al.*, 1976; Mauritz *et al.*, 1979).

Bilateral stimulation of the tibial nerves was performed simultaneously in both popliteal fossæ. The small cathodes were fixed directly over the tibial nerves and the large anodes over the patellæ (Hugon, 1973). Stimulus duration was 1 ms. Stimulus strength was adjusted to evoke a half-maximal H-reflex without any larger M-response. M- and H-responses were exclusively seen in the gastrocnemii and not in the anterior tibial muscles.

Electromyographic recording was by bipolar surface electrodes fixed over the anterior tibial muscles and the gastrocnemius/soleus muscles. The EMG was continuously monitored during experiments. For further processing the EMG was rectified and filtered (time constant of the rectifier: 10 ms, filter time constant 1 ms).

Averaging of sway responses and of the rectified EMG was performed with a Nicolet averaging computer (Model 1072). The averaged curves were plotted on a x-y recorder (Hewlett Packard, Model 7044 A).

Fourier analysis of postural sway components was done on a digital computer (IBM 1130) with a program developed by Allum (*see* Allum, Dietz and Freund, 1978; Dichgans *et al.*, 1976). After analog to digital conversion with a sample rate of 100/s, 37 second-segments were analysed. Lateral and anteroposterior components of body sway were separately passed through a digital Butterworth low pass filter by which all oscillations above 12 Hz were damped to eliminate noise. In a few instances a commercially available online fast-Fourier-analyser (Nicolet 444 A computing spectrum analyser) was used.

PATIENTS

Recordings were taken from 7 patients with late cortical cerebellar atrophy and 14 normals as controls. Patients aged between 42 and 62 years had been admitted to hospital because of gait and postural ataxia, usually accompanied by ataxia of the lower limbs and oculomotor deficiencies of varying degrees. All of them showed the 3 Hz anteroposterior postural tremor in the Fourier power spectrum of sway, at least when standing with the eyes closed. The relevant clinical features of these patients were documented in a preceding paper (Mauritz *et al.*, 1979). The normal subjects were carefully examined by a neurologist before testing.

PROTOCOL

Subjects were placed on the platform with the feet in a pre-set position (heels separated 4 cm and feet splayed at an angle of 30 degrees) and instructed to stand as still as possible. Experiments began with a 60 s recording of spontaneous sway with eyes open and then with eyes closed. Subsequently the tibial nerves were stimulated while the subjects stood with their eyes closed or open and sway parameters as well as EMG were recorded. Stimulus intensity was increased until the H-reflex reached its maximum. The stimulus strength used for our long-loop reflex examination was then adjusted to evoke a half maximal H-reflex. By this stimulus small M-responses were evoked occasionally. It can therefore be assumed that under these conditions predominantly Ia afferents were stimulated. The responses of 16 stimuli were averaged. Stimuli were randomly presented and the stimulus interval was not less than 4 s. In addition the influence of different stimulus strengths (maximal, half-maximal, supramaximal and near threshold for the H-reflex) was tested in 5 normal subjects.

RESULTS

I. Stimulus Responses in Normals

After bilateral stimulation of the posterior tibial nerves, half-maximal H-reflexes of both triceps suræ are evoked. The consequent reaction is a rapid forward displacement of the centres of foot pressure (CFP). (The displacement of CFP is not equivalent to the shift of the centre of gravity but entails dynamic components (Gurfinkel, 1973)). This torque response starts 45 to 50 ms after onset of stimulus. The maximum of the forward displacement of the centre of force occurs 140 ms after stimulation (SD ± 14 ms). Due to the reaction force a more tonic backward sway of CFP follows (fig. 1). In compensation for the late backward displacement of CFP the head and trunk are automatically flexed forward, thereby stabilizing posture.

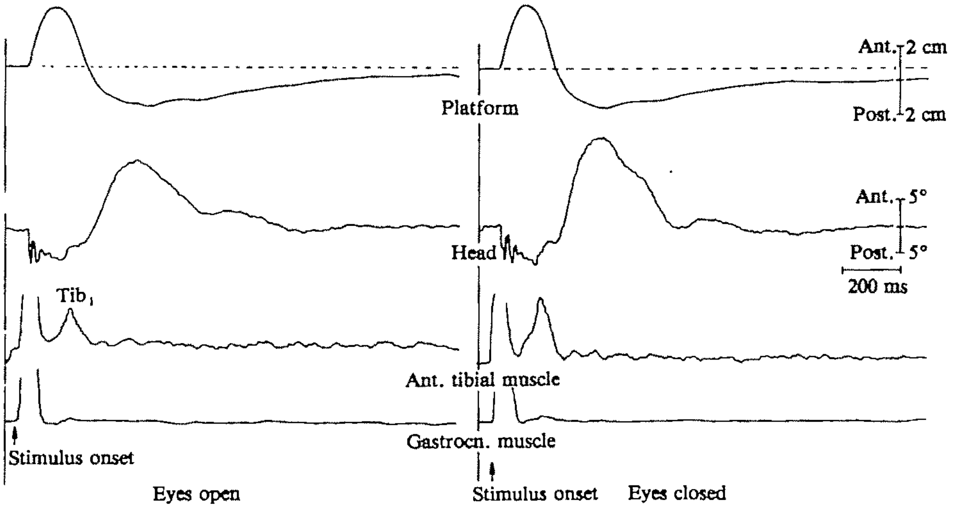

FIG. 1. Averaged stimulus responses of centre-of-force displacements (platform), anteroposterior head inclinations (head) and rectified EMG-responses of the anterior tibial and gastrocnemius muscles in a normal subject with eyes open and eyes closed ($n = 16$). The initial gap in the EMG recordings includes the high amplitude stimulus artifact, and, in gastrocnemius only, the M-response and H-reflex. The H-reflex causes a forward displacement of the CFP followed by slow and long lasting backward sway. The synchronous late discharge of the tibial muscle (tib_1) has a higher amplitude with eyes closed. The gastrocnemius muscle shows almost no late discharge.

The early backward movement of the head is passive. The amplitude of the centre-of-force displacement varies in different subjects, mostly due to the varying maximal forces of their triceps suræ.

A most conspicuous finding is a *late synchronized discharge in the anterior tibial muscle* (*tib*$_1$), which is seen in all normal subjects. Its average latency of onset is 120 ms (SD ± 20 ms; n = 14) after the stimulus. The latency of the tib$_1$ discharge can easily be defined because the resting activity during standing is almost zero in this muscle (Joseph, 1960). The amplitude of this late discharge increases in most subjects when the eyes are closed, as exemplified in fig. 1. A more detailed study (Schmitt, 1980) demonstrated that the tib$_1$ amplitude depends on the rate and amplitude of the forward CFP displacement (fig. 2). The duration of this late synchronized discharge averaged 90 ms (SD ± 19 ms).

Ankle angle measurements (fig. 3) reveal that backward sway and therefore stretch of the anterior tibial muscle by gastrocnemius-soleus contraction starts either 50.5 (SD 8.8) ms or 80 to 90 ms after stimulation, while CFP displacement is

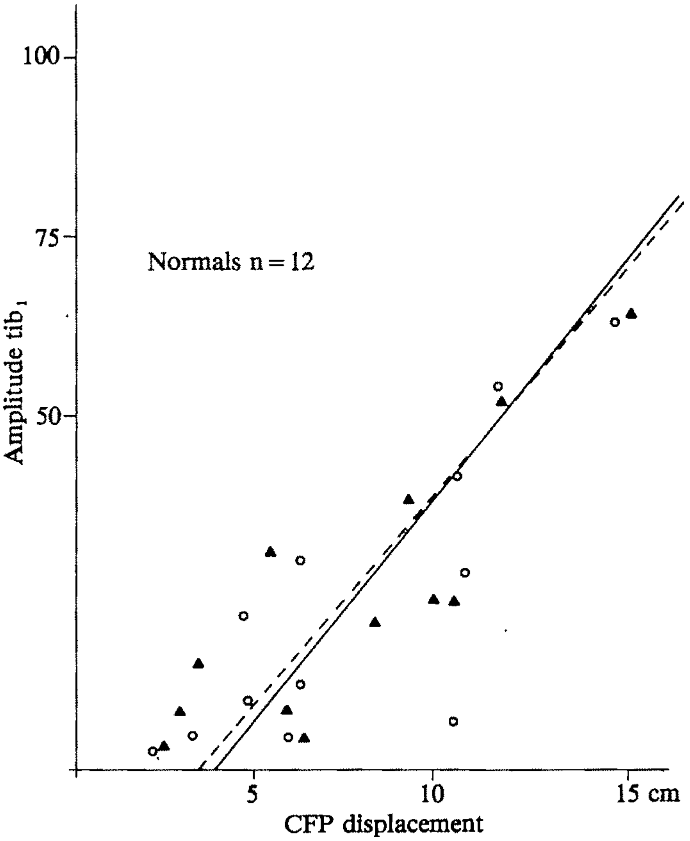

FIG. 2. Tib$_1$ amplitude (ordinate) increases roughly linearly with CFP displacement (abscissa). ○ = eyes open. ▲ = eyes closed.

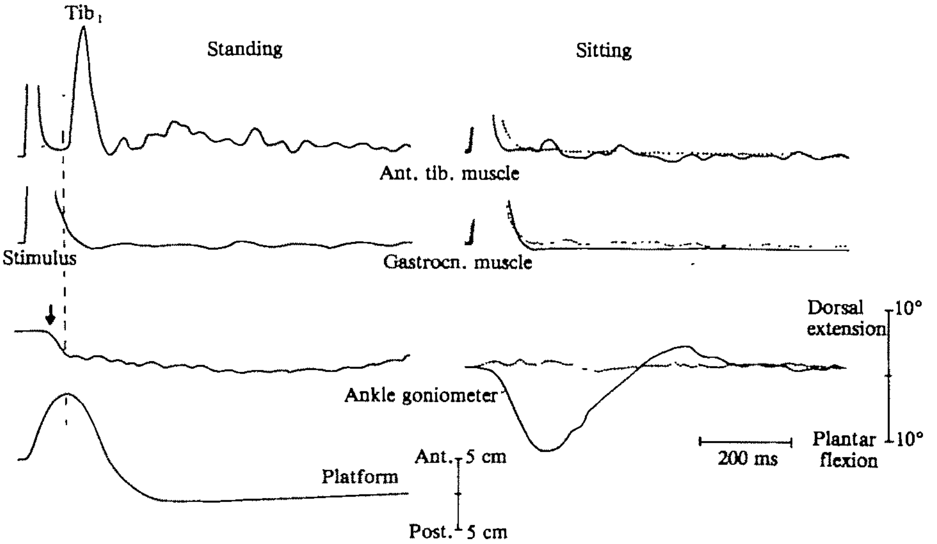

FIG. 3. Average stimulus responses (n = 16) in a normal subject during standing (*left*) and sitting (*right*) under isometric (......) and isotonic conditions (——). Note that there is no tib₁ discharge while sitting, although the anterior tibial muscle stretch exceeds that during standing.

still forward. The 50 ms latencies are observed when both M- and H-responses occur in the gastrocnemius muscle. The 80 ms latency is observed when, at weaker stimulus intensities, only H- but no M-responses are elicited (*see* Methods). Stretch of the anterior tibial muscle by H-reflex activity after 30 to 40 ms is followed by the tib_1 discharge. Its latency with respect to muscle stretch is compatible with the assumption that tib_1 is a *segmental stretch reflex response*. The assumption of a segmental stretch reflex response is supported by the observation (fig. 6) that with supramaximal stimuli when M-responses occur exclusively and H-responses are occluded, tib_1 latencies are shortened by an amount roughly equal to the time interval between M- and H-responses (24 to 35 ms).

In 6 out of 14 normals tib_1 was followed by a second late discharge (tib_2), of smaller amplitude, at an average interpeak interval of 90 to 120 ms to tib_1 (fig. 4). Three normals even showed a third discharge (tib_3) of still smaller amplitude but similar interpeak interval. The reason for these inter-individual differences in amplitude and number of late discharges could not be determined in our experiments. With regard to their nature, tib_2 and later discharges are considered to be *long-loop reflexes*, and, in normals, are certainly not aroused by stretch of the tibial by contraction of the gastrocnemius muscle.

Late synchronized activity in the gastrocnemius-soleus muscle, as opposed to tib_1 in the tibial muscle, is found inconsistently. It occurred occasionally in 7 out of 14 normals. If present, it sometimes appeared roughly simultaneously with tib_1. In other cases it was definitely delayed by 29 to 60 ms with respect to the onset of tib_1. A second late discharge in the soleus (gastroc_2) was found in only 3 persons.

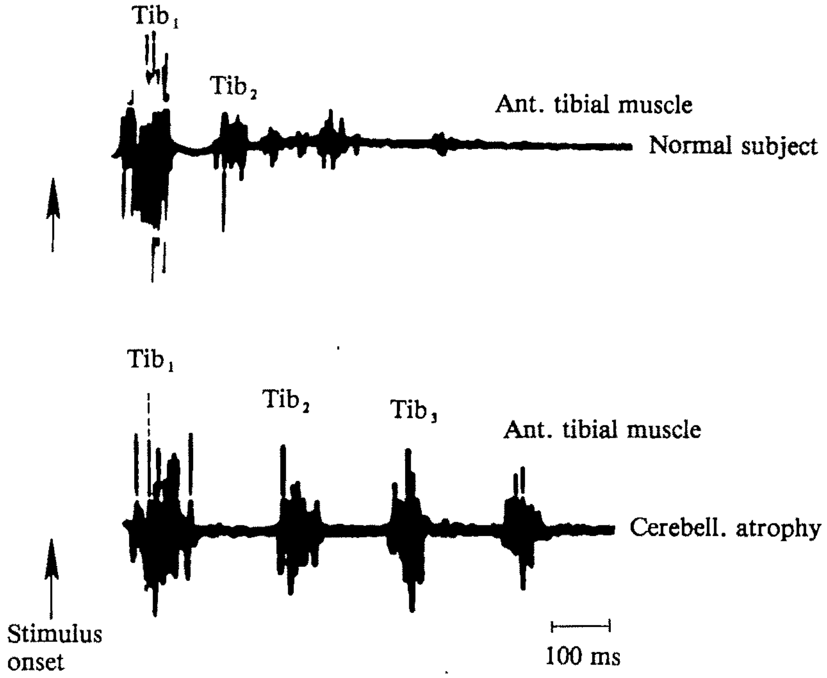

FIG. 4. Original recording of synchronized anterior tibial muscle discharge after stimulation of both tibial nerves in a normal subject (*upper trace*) and a patient with late cerebellar atrophy (*lower trace*). Note the increased interval between tib$_1$ and tib$_2$ in the patient. The slight increase in latency of tib$_1$ (+15 ms) in the patient is not significant when considering the entire population.

Late discharge in different postures. To further test the assumption that tib$_1$ is a segmental stretch response, experiments were performed with different postures. Whereas tib$_1$ was prominent in normals standing upright, it could not be evoked in the sitting position, either with isometric (fixed ankle angle) or with isotonic (free ankle) contraction (fig. 3, right half). It may be noted that even in a subject sitting with the ankle free, and in spite of an enormous plantarflexion and stretching of the anterior tibial muscle, no tib$_1$ discharge occurs. This result does not necessarily argue against the assumption that tib$_1$ is a spinal stretch reflex, since excitability in the motoneuron pool and descending driving activity is smaller in the sitting position. Support for this view comes from experiments in which motoneuron excitability in the standing subject was manipulated by the following procedure. Normal subjects were instructed to lean forward, so that their centre of gravity projected 5 cm anterior to their normal position. This was achieved by the instruction to match with their average position of CFP a given line on the monitoring oscilloscope. When subjects were leaning forward, tib$_1$ was invariably reduced in amplitude, and in three subjects was not observed at all (fig. 5). Instead of this reduced tib$_1$ discharge the late soleus discharge was increased. Leaning

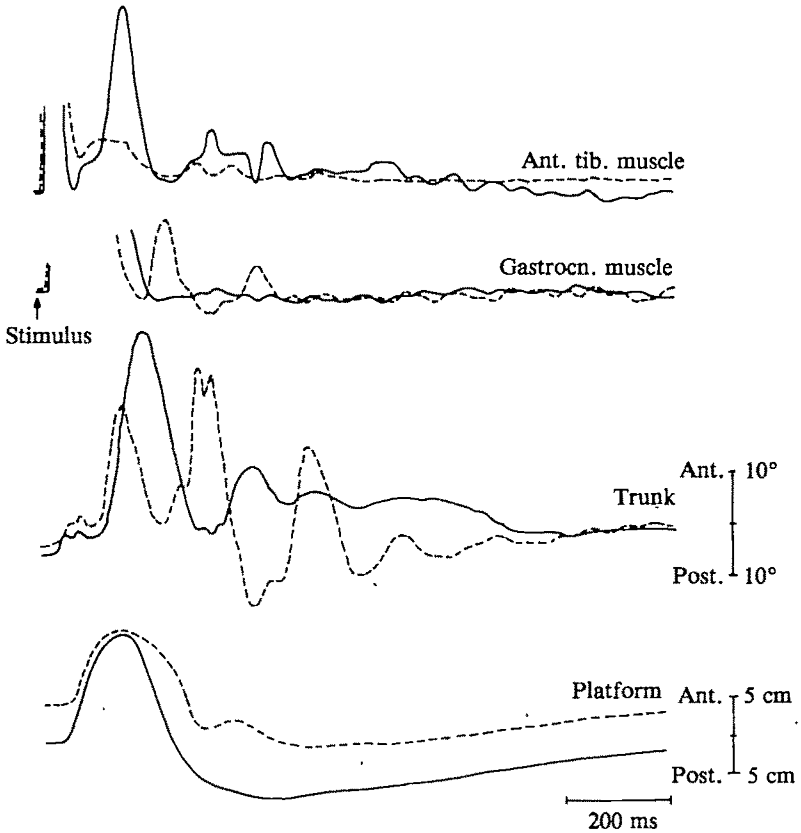

FIG. 5. Averaged stimulus-responses ($n = 16$) in a normal subject standing upright (——) and leaning forward, so that the CFP projects 5 cm anterior to the averaged normal position (......). Tib_1 and the stimulus induced displacement of the CFP decrease while leaning forward whereas the gastrocnemius response is quite expectedly enhanced.

backwards yields the opposite modulation of the response. In the normal standing position neither tib_1 nor the later discharges (tib_2 and tib_3) could be modulated by instructions like 'resist' the electrically-induced sway or 'let sway'. This is in agreement with Iles (1977) who also used electrical stimuli.

Dependence of tib_1 on stimulus strength. In five subjects the relation between the amplitude of the tib_1 discharge and the stimulus strength was investigated by applying four different stimulus strengths: threshold level, half-maximal, maximal and supramaximal stimuli for the H-reflex in gastrocnemius. By a supramaximal stimulus only an M-response could be elicited. Due to antidromic collision no H-reflex could be evoked (fig. 6; dotted tracing). There was a correlation between stimulus strength on the one hand and ankle angle displacement and torque amplitude on the other, and, thus, a correlation between tibialis stretch and the amplitude of the tib_1 response (figs. 2 and 6). The correlation between the amplitude of the H-reflex and the amplitude of tib_1 is good as long as the H-reflex increases. Tib_1 further increases with supramaximal stimuli, when due to collision no H-reflex can be seen but a large M-response is evoked. At supramaximal stimulus intensities the M-response causes the stretch and the consequent tib_1. Accordingly the latency of tib_1 decreases by an amount equal to the interval between M- and H-responses (fig. 6). These results again suggest a direct dependence of tib_1 on the developed force of the gastrocnemius muscles and therefore on the consequent stretch of the tibial muscles.

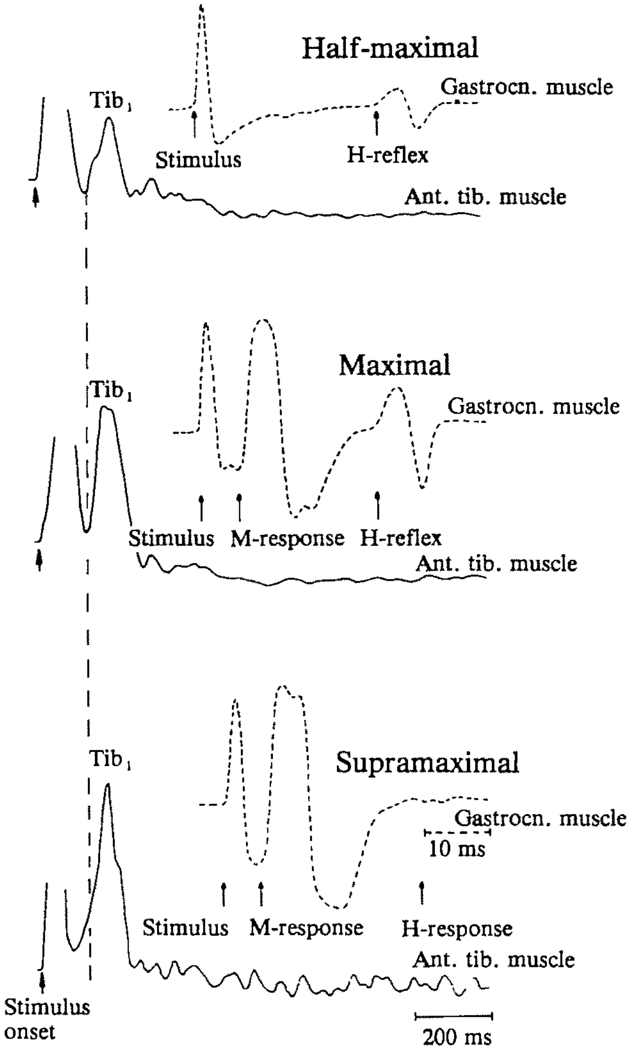

FIG. 6. Influence of increasing stimulus voltage upon amplitude and latency of tib_1. Dotted line illustrates M- and H-responses of gastrocnemius on an expanded time-scale. Note increasing amplitude of tib_1 as the M-response increases. Also note shorter latency of tib_1 (roughly 35 ms) when only the M- and not the H-response occurs. Stimulus strength was about half-maximal for H-reflex (*top*), maximal (*middle*), and supramaximal just abolishing the H-reflex by collision (*bottom*).

Afferents responsible for the tib_1 *discharge.* To exclude the possibility that late EMG responses were flexor reflexes, triggered by painful stimulation of cutaneous receptors, the stimulating electrodes were displaced a few centimetres in the popliteal fossa or were applied to several places on the leg and foot. Stimulus intensity was increased until it was almost intolerable. This procedure elicits no motor reactions as monitored by EMG (fig. 7).

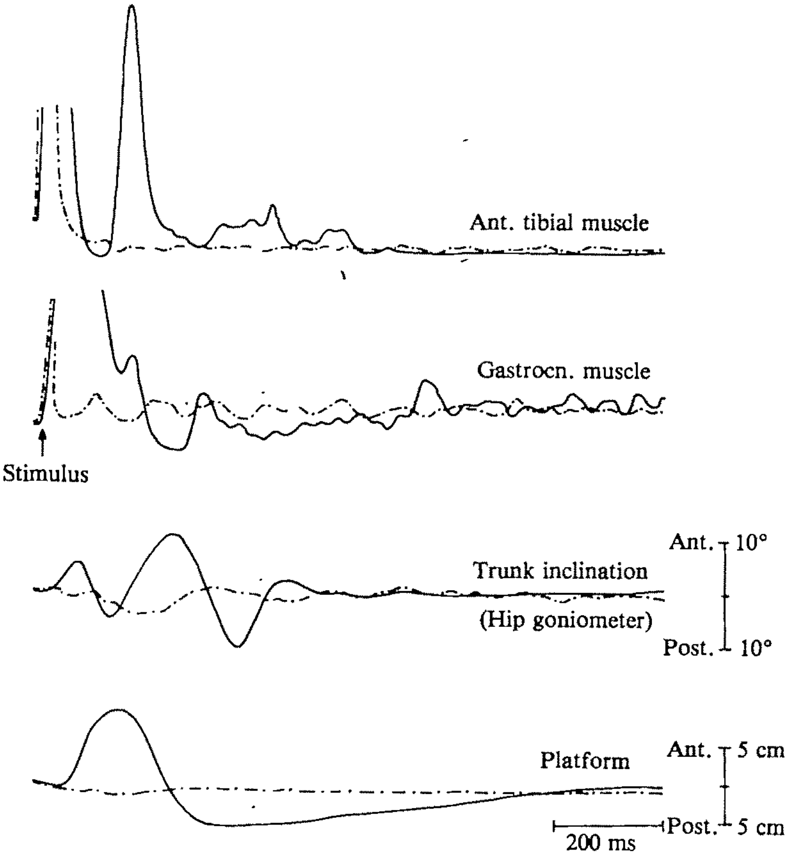

FIG. 7. Motor nerve stimulation (——) elicits tib_1 but cutaneous stimuli (.—.—.) do not (normal subject).

In a few other experiments Ia-afferents were blocked by ischæmia of both thighs for approximately 20 to 25 min (Magladery, McDougal and Stoll, 1950; Schenck and Bayer, 1951). This method first blocks large fibres and therefore blocks proprioception before motor innervation and pain perception. Somewhat higher stimulus strengths were used in these experiments to obtain an M-response in addition to the H-reflex. The amplitude of this M-response assured and controlled that the motor axons remained unblocked. Fig. 8 demonstrates the results obtained in one of these experiments. It was found that the amplitude of tib_1 decreases markedly. Due

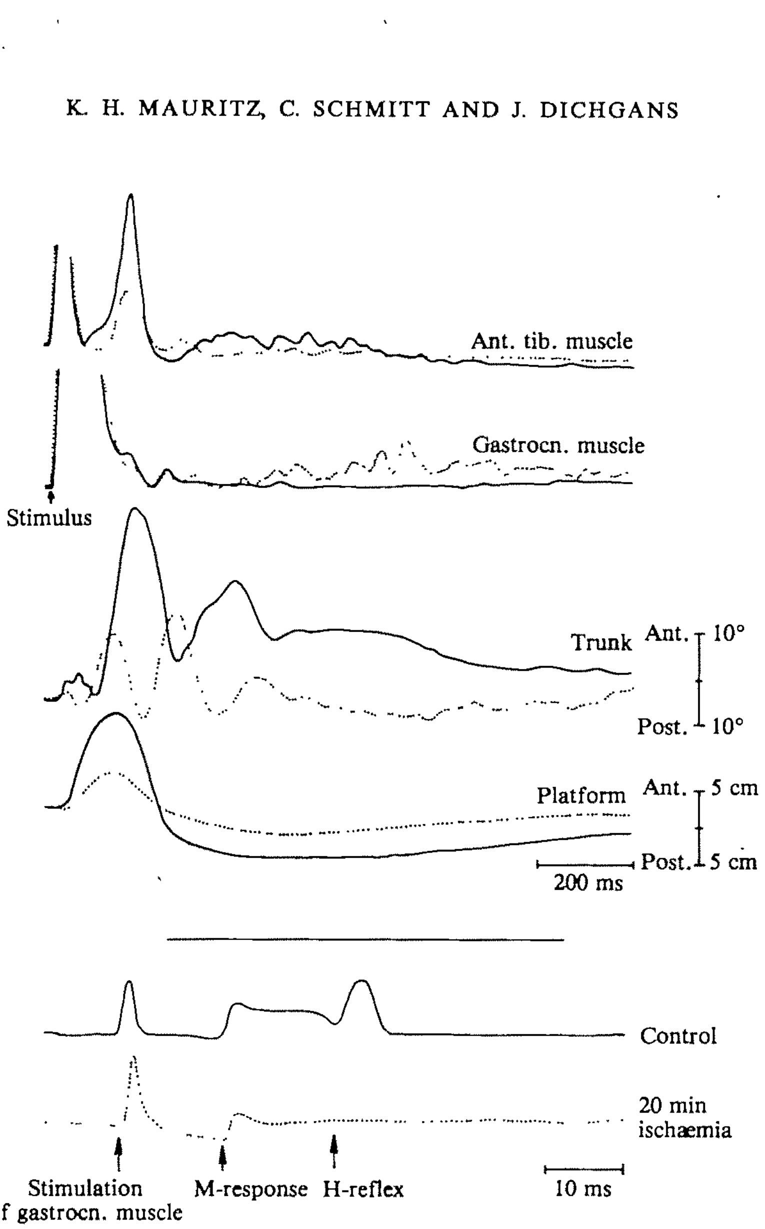

FIG. 8. Effects of bilateral partial blocking of Ia afferents by 20 minutes ischæmia of both thighs upon tibialis anterior and gastrocnemius discharges (------) in comparison to normal stimulation (——). Averages of 16 stimuli. The two bottom traces depict the M- and H-responses before and after 20 min of ischæmia. The stimulus strength was chosen such as to evoke M- and H-responses in controls. Ischæmia abolishes the H-response and decreases tib_1 as well as the CFP displacement, while the M-response is only minimally diminished. Maximal voluntary force (not depicted) is unchanged.

to the absence of the H-reflex the torque exerted on the platform also decreases. To further support the segmental stretch reflex nature of tib_1, stretch was reduced in three subjects by imposing a 30 kg load on the trunk and thereby increasing the body's inertia and decreasing the ankle displacement. Although the electrical stimulation of tibial nerve afferents is unchanged by this procedure the amplitude of

tib_1 is reduced, which supports the conclusion that tib_1 is not the direct response to afferent electrical stimulation but requires stretch of the tibial muscle and therefore displacement.

II. Stimulus Responses in Patients with Anterior Lobe Cerebellar Atrophy

Synchronization of postural tremor after electrical stimuli. In patients with anterior lobe atrophy the average responses of the centre of force after randomly applied electrical stimuli to both tibial nerves show well-defined oscillations of the same frequency as the spontaneous postural tremor. Thus the stimulus synchronizes the phase of ongoing oscillations, indicating afferent control of the postural tremor. Exceptions were only occasionally observed and are exemplified in trace 3 of fig. 9 on the right. When the eyes are open the body oscillations are damped. Without visual stabilization, the oscillations show larger amplitudes (fig. 9).

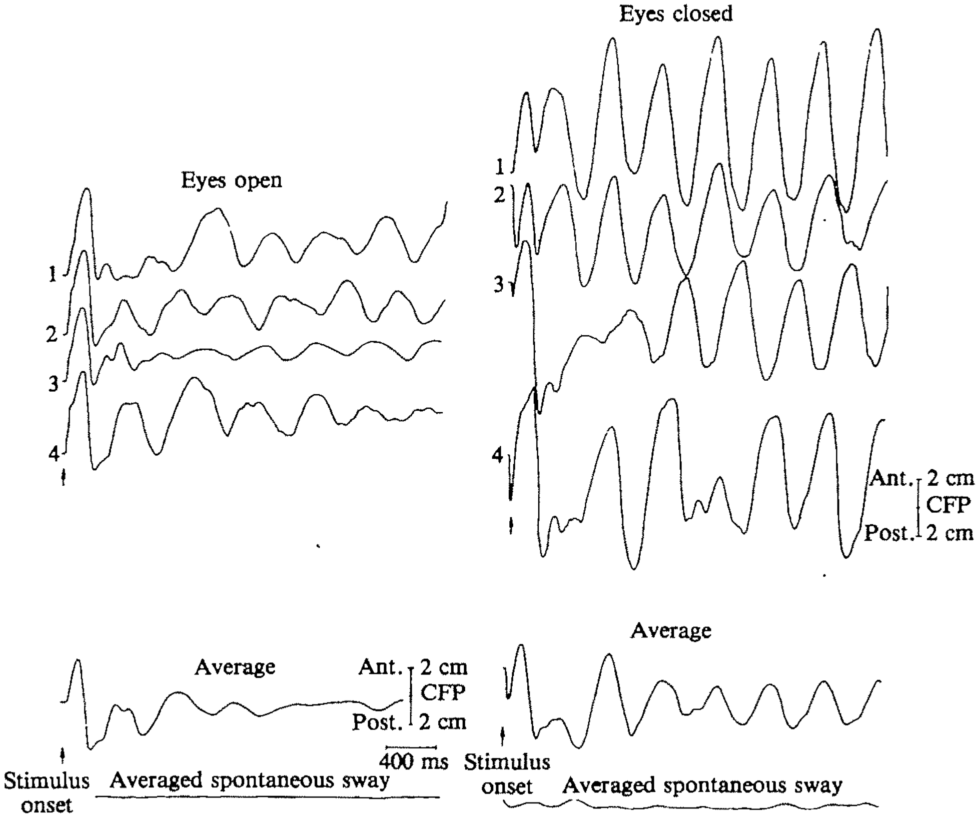

FIG. 9. Synchronizing effect of electrical stimulation of both tibial nerves upon anteroposterior postural sway in a patient with anterior lobe atrophy. Sixteen stimuli were randomly presented with eyes open (*left side*) and eyes closed (*right side*). *Above*: four examples of individual post-stimulus traces of the CFP recording; *below*: averaged post-stimulus response (CFP) and the averaged spontaneous sway. Note the occasional failure in synchronization (trace 3 on the *right*).

In contrast to the response of normal subjects, the stimulus invariably evokes rhythmical synchronized discharges in the anterior tibial muscle in patients with cerebellar atrophy (fig. 4, lower trace). In these patients we observed at least two, in most instances several and frequently a sustained sequence, of tibial muscle discharges in the averaged curves (fig. 11). Eye closure increased the amplitude and duration of these discharges. In both patients and normals tib$_1$ has an average latency of 117 ms (SD ± 17; n = 7). The average interval to the second discharge, however, is significantly longer than in normals and averages 200 ms (up to 380 ms in one rare exception). The time intervals between tib$_1$ and tib$_2$ and the following synchronized muscle discharges is therefore 80 ms (up to 250 ms) longer than in normal subjects. As can be seen in fig. 10 an alternating discharge between the tibial

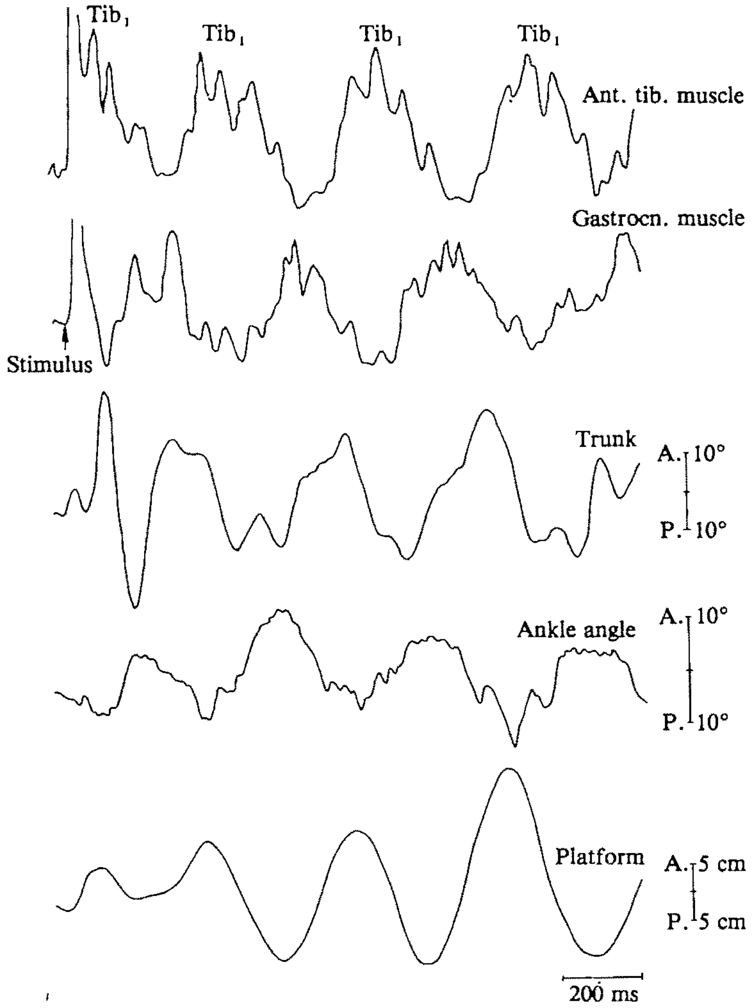

FIG. 10. Stimulus-induced anteroposterior postural tremor in a patient with longstanding cerebellar atrophy with eyes closed; from top to bottom: rectified EMG of anterior tibial and gastrocnemius muscles, trunk inclination, ankle angle and CFP displacements.

and gastrocnemius muscles is frequently observed in these patients (but not in normals). We think that the alternation of discharge in flexors and extensors constitutes and sustains the postural tremor. The contraction of the anterior tibial muscle causes the CFP on the platform to move backwards rapidly and with short latency, because the body inertia brings the leg (measured as ankle angle) forward. This forward movement stretches the gastrocnemius and thereby elicits its contraction, and so on. The tremor seems to be the consequence of reflex facilitation. Tremor frequency seems to depend on the loop-time, which is prolonged in this disease, and increases with progression of the atrophy while tremor frequency decreases. Other forms of postural tremor, for example, parkinsonian tremor or tremor in Wilson's disease, cannot be synchronized by this technique.

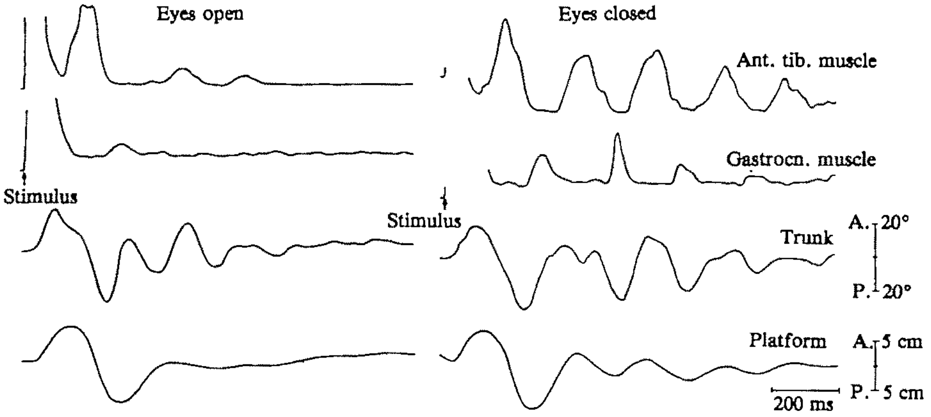

FIG. 11. Provocation of rhythmical discharges in the anterior tibial muscle (tib$_1$, tib$_2$ *et seq.*) by simultaneous electrical stimulation of both tibial nerves in a standing patient with incipient anterior lobe atrophy. Note that the rhythmical discharge can only be evoked during eye closure. A damped anteroposterior oscillation is also seen in the platform registration and in the trunk movement.

In patients with incipient disease, when spontaneous postural tremor cannot be detected clinically, the anteroposterior oscillation can be elicited by mechanical stimuli, that is, rapid tilt of the supporting platform (Mauritz *et al.*, 1979), and also by electrical stimulation. Fig. 11 gives an example. It shows a rapidly damped oscillation which is almost undetectable with eyes open (compare with fig. 1 from a normal subject). The intervals between the rhythmical discharges of the tibial muscle average 180 ms and were therefore between those of normals (120 ms) and of patients with the full-blown clinical syndrome (up to 380 ms).

In patients with incipient disease, rhythmical discharges of gastrocnemius are absent or considerably smaller than those of the tibial muscle.

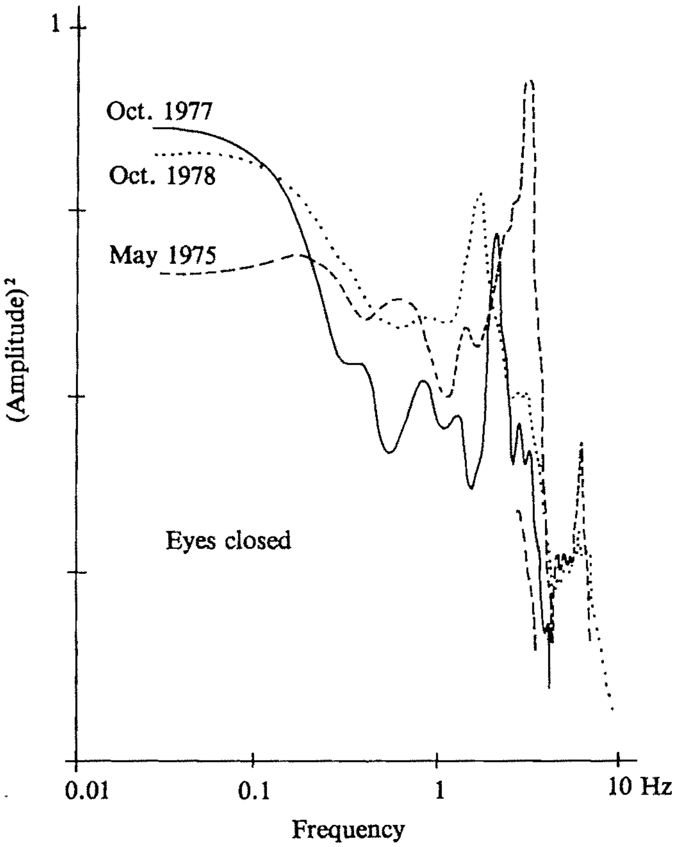

FIG. 12. Anteroposterior sway. Dominant tremor frequency at different stages of progressive anterior lobe atrophy observed over three and a half years (Fourier power spectra).

Decay of tremor frequency with further degeneration. We had the opportunity to re-test 5 patients over a period ranging from one to four years. In 2, Fourier analysis of postural sway was performed. In 3 patients repeated post-stimulus recordings are available in addition. In all these re-tested patients the clinical symptoms of stance and gait ataxia had increased more or less and tremor frequency had decreased. Correspondingly the interval between tib_1 and tib_2 and later intervals had increased.

Fig. 12 demonstrates this frequency decay in one patient over a period of three and a half years. In this patient the frequency shift from 3.5 to 2.3 Hz corresponds to an increase of 149 ms in loop-time latency. So far we have the impression that the severity of the disease correlates with the length of the tib_1-tib_2 interval. This assumption is also supported by a correlation of the sway path length per unit time and tib_1-tib_2 interval.

DISCUSSION

The main findings in this study of patients with late cortical cerebellar atrophy are the delayed, repetitive and increased long latency responses (tib_2, tib_3 etc.) to a single electrical stimulus to the tibial nerves in the antagonistic anterior tibial muscles. The tib_1 response is not delayed. The responses in the agonistic gastrocnemius muscles are more variable. The alternating activity of the gastrocnemius and tibial muscles results in postural tremor of the body. In incipient cases of cerebellar atrophy this tremor may be evoked by electrical stimulation of the tibial nerves, and if spontaneously present this tremor can be synchronized.

We interpret this postural tremor as the consequence of an increased gain and loop-time within suprasegmental pathways. In normal subjects, both segmental and suprasegmental reflexes are evoked in the anterior tibial muscles when these are

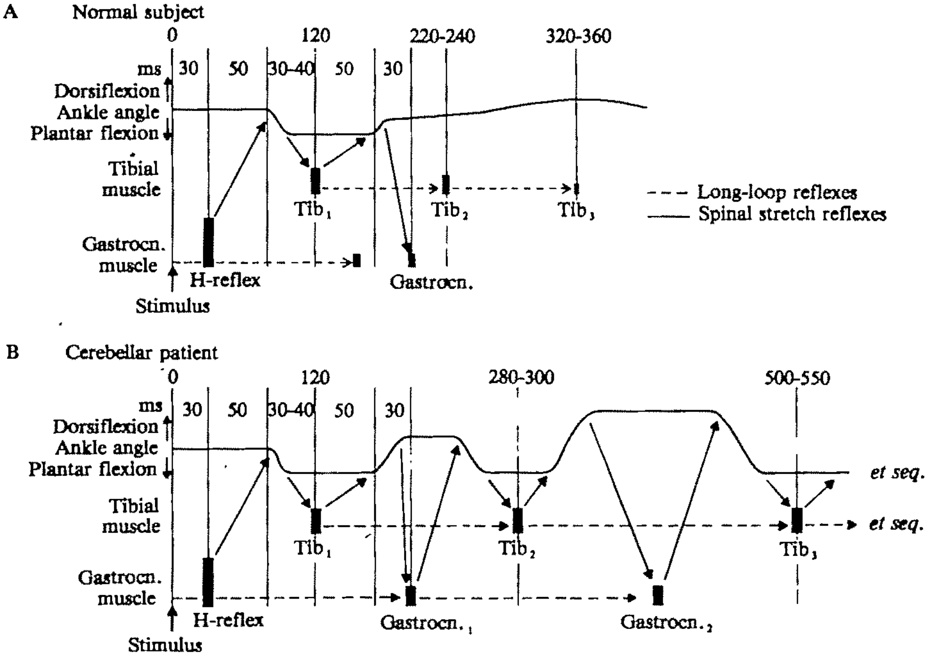

FIG. 13. Schematic presentation of post-stimulus responses and of the postural tremor mechanism. Further explanation in text. A, *normal subject*. A single shock to the tibial nerve evokes an H-reflex in gastrocnemius, latency 30 ms, which is followed by a late (long-loop) reflex (- - - →). The H-reflex plantarflexes the ankle (———→) and thus stretches the anterior tibial muscles, activates their Ia afferents, and evokes a stretch reflex (———→ tib_1). Tib_1 dorsiflexes the ankle (———→), stretches gastrocnemius, and elicits a segmental stretch reflex (———→ gastrocn). This stretch reflex is not synchronous with the late (loop-loop) reflex in gastrocnemius. Tib_1 is followed by repetitive long-loop reflex activity (tib_2, tib_3). B, *patient with cerebellar atrophy*. Events of the first 120 ms as in A. The late (long-loop) reflex in gastrocnemius is delayed (- - - → and $gastrocn_1$), so that its effect is synchronous with that of the segmental stretch reflex evoked by tib_1 (———→ and $gastrocn_1$). The Ia afferents of gastrocnemius are stretched, eliciting a stretch reflex which plantarflexes the ankle and elicits tib_2 (———→), plus a second delayed reflex in gastrocnemius (- - - →, $gastrocn_2$). Tib_1 is also followed by a delayed long-loop reflex (tib_2), which is synchronous with, and enhanced by, the segmental reflex evoked in the tibial muscles by the reflex contraction of gastrocnemius ($gastrocn_1$ and ———→). The stretching of gastrocnemius by tib_2 (———→) is synchronous with the action of the long-loop gastrocnemius reflex ($gastrocn_2$). The powerful alternating contractions ($gastrocn_2$, tib_3, *et seq.*) sustain the further tremor.

stretched by contraction of the gastrocnemii and *vice versa* (*see* fig. 13A); but these two reflex activities are not synchronized. In patients with cerebellar atrophy segmental and suprasegmental mechanisms may add to each other: due to their latency increase, the long-loop reflexes synchronize with the segmental monosynaptic reflexes thereby augmenting the motor responses (fig. 13B). This conforms with results of Villis and Cooke (1976), who observed large M_2 responses only if motor activity over long and short pathways coincided in time.

The late synchronized discharge in the anterior tibial muscle (tib_1) occurs with a latency of 120 ms after stimulation of the tibial nerve, which means 40 to 60 ms after stretch of the anterior tibial muscle. This latency is compatible with the assumption of a *spinal stretch reflex*, considering mechanical delays of body inertia and stiction and taking into account that a certain threshold for exciting the muscle receptors in the tibial muscle must be achieved. The latency of 120 ms is also compatible with the assumption of a *long-loop reflex* (Melvill-Jones and Watt, 1971; Burke and Eklund, 1977; Nashner, 1976). This reflex then would be the response either to afferent stimulation of the tibial nerve or the response to electrical stimulation of the peroneal nerve. The last possibility was excluded by the lack of M- and H-responses in the tibial muscle. A long latency component due to direct afferent stimulation of the tibial nerve as suggested by Taborikova (1973), however, could not be excluded.

The important fact that tib_1 is unchanged in gain- and loop-time in cerebellar patients compared to normals shows that tib_1 does not depend on intact cerebellar function. The pathways that are responsible for tib_1 cannot also be responsible for tib_2, tib_3 . . . tib_n. We have shown that tib_1 is mediated by segmental components predominantly. This evidence is strengthened by two further results which prove the dependency of tib_1 on stretch of the anterior tibial muscle. These results are (1) decrease of tib_1 with increased load on the body and therefore decreased ankle angle displacement; and (2), diminution with decreased muscle tension when the subject is leaning forward.

That tib_1 is not vestibularly elicited by head displacement induced by the stimulus is suggested by its latency which is considerably shorter than that observed by Nashner (1976).

We suggest that in the normal subject tib_2 is a long-loop reflex response to the stretch of the tibial muscles. This assumption is based on its latency (about 150 to 160 ms). This long latency is appropriate for a long-loop reflex when one considers the very slow velocity of stretch of the anterior tibial muscles and the fact that the response of the stretch receptor may be delayed with such low velocities. A segmental component of tib_2 can be excluded by the absence of a stretch response of the gastrocnemius to tib_1. The reflex contraction of gastrocnemius would in turn stretch the tibialis and thereby evoke a second segmental response in this muscle, as in the cerebellar patient.

Long-loop reflexes of comparable latency have been observed in leg muscles by Nashner (1976) and Chan, Melvill-Jones and Watt (1979). Because these long latency discharges could not be elicited in patients with spinal transsections (Chan *et al.*, 1979) nor in patients with restricted postcentral or capsular lesions (Marsden, Merton, Morton and Adam, 1978; Lee and Tatton, 1975) a transcortical long-loop was postulated, as earlier suggested by Hammond (1960) and Phillips (1969). These results in humans are in conflict with findings in cats, who still show long latency responses after high spinal transection (Ghez and Shinoda, 1978; Ahlmann Grillner and Udo, 1971). Experiments in animals suggest that the cerebellum is part of a long latency loop (Murphy *et al.*, 1973, 1975*a*, *b*). Murphy and his co-workers postulated multiple parallel channels to the motor cortex for proprioceptive information from the muscles. They found a fast lemniscal pathway for Ia-afferents to the motor cortex and a transcerebellar pathway with a longer latency and a higher threshold for a combination of Ia, II and Ib fibres *via* the nucleus interpositus and the ventrolateral thalamus to the motor areas of the precentral cortex. In accordance with Conrad and Brooks (1975), Meyer-Lohmann, Conrad, Matsunami and Brooks (1975) and Villis and Hore (1977), showed that the second late response of the motor cortex only, which is seen in connection with M_3, was influenced by reversible cooling of the intermediate part of the cerebellum. Patients with cerebellar lesions were earlier shown to have delayed long-loop reflexes (Marsden, Merton and Morton, 1977; Nelson and Lance, 1978). Marsden *et al.* (1977) observed a delay in long latency responses for the significantly shorter long-loop times in the upper limb (difference about 60 ms; *see* Chan *et al.*, 1979). These results are comparable with ours.

Theoretically, 3 Hz oscillations in a neuromuscular system can occur simply as the result of an increased loop-time (Stein and Oguztöreli, 1976).

SUMMARY

The pathophysiology of postural tremor was studied in 7 patients with cortical cerebellar atrophy, and compared with the responses of 14 healthy control subjects to the same tests. Both tibial nerves were simultaneously and selectively stimulated in the fossa poplitea. EMG was recorded from agonist gastrocnemius muscles and from the antagonistic anterior tibial muscles. Displacement of the centre of foot pressure, inclination of trunk and head in the anteroposterior direction, and the ankle angle were also measured.

Patients and controls both exhibit a synchronized discharge in the anterior tibial muscle (antagonist) with a latency of 120 ms to stimulus onset (tib_1). Tib_1 is shown to be a segmental stretch reflex elicited by the contraction of the gastrocnemius (agonist).

A later, presumed long-loop response occurs after another 120 ms both in gastrocnemii and anterior tibial muscles in the normal subjects. This latency, and the amplitude of the late reflex, are increased in the patient group. The synchronization of delayed long-loop reflexes and a stretch response of the gastrocnemius in

response to tib_1 terminate the first cycle of the postural tremor which thereafter continues by way of the same mechanism generating a contraction of the anterior tibial muscle.

Postural tremor can thus be synchronized by a single bilateral electrical stimulus and can even be elicited in incipient cases of the disease. With further progression of the cerebellar atrophy the dominant frequency of the postural tremor decreases along with an increase of long-loop latencies.

ACKNOWLEDGEMENTS

We are grateful to Mrs Ulrike Römmelt, Mr Kapp and Mr Brenneisen for technical assistance. The work was supported by the Deutsche Forschungsgemeinschaft (SFB 70-Hirnforschung und Sinnesphysiologie).

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(*Received May 8, 1980*)

Brain (1981), **104**, 117–128

THE EPIDEMIOLOGY OF APHASIC AND COGNITIVE IMPAIRMENT IN STROKE

AGE, SEX, APHASIA TYPE AND LATERALITY DIFFERENCES

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INTRODUCTION

PUBLISHED reviews of aphasic populations had not shown significant differences between the ages of various types of aphasics (Kertesz and Poole, 1974; Pizzamiglio, Appicciafuoco and Razzano, 1976), or fluent and non-fluent aphasics (Brust, Shafer, Richter and Brunn, 1976) until the issue of age and aphasia type was raised again in the literature recently (Obler, Albert, Goodglass and Benson, 1978). They chose 167 right-handed males with cerebrovascular accidents who received an 'unequivocal' diagnois of either Broca's, Wernicke's, anomic, conduction or global aphasia. The time from onset was not defined. Compared to the median age of the total group (55.8 years), patients with Broca's aphasia were significantly younger (median age 51 years) and Wernicke's aphasics were significantly older (median age 63 years). They suggested that progressive bilateral frontal atrophy seen in ageing may be associated with a disinhibition of verbal output. Brown and Jaffe (1975) proposed a hypothesis that a continuing differentiation of function between the hemispheres and within the left hemisphere with age would result in more aphasic syndromes with comprehension difficulty in older patients. Another possible explanation for the younger age of Broca's aphasics in some surveys is that some of the patients were examined in a more chronic stage. Older patients with severe global aphasia may have decreased survival, leaving the younger patients in the chronic group to evolve to Broca's aphasia. This underlines the importance of considering the time since onset as a major factor in the epidemiology of cognitive impairment. More accurate information may be obtained from data in an acute population such as in our study.

Sex differences between aphasics on the whole have not been significant among the majority of surveys (McGlone and Kertesz, 1973; Brust *et al.*, 1976). Higher incidence of non-fluent aphasia was found in males by Brust *et al.* (1976) but the types were defined clinically and the majority were classified as 'mixed' aphasics with significant deviation from the usually accepted categories. Lansdell and Urbach (1965) found lower verbal scores in non-aphasic men after temporal lobe removals than in women although the size of the lesion was an added factor. McGlone (1977) found decreased verbal IQ in non-aphasic males with left brain damage when compared to females who in turn had lower verbal IQs than the males when the right hemisphere was damaged. She found only 2 aphasics in a sample of 16 left hemisphere lesions in women. From this evidence she concluded that aphasia is associated with damage to the left hemisphere less often in females and that speech organization shows a more 'heterogenous pattern' in females, presumably a more bilaterally distributed speech representation.

Sex differences in cerebral dominance are controversial. Kimura (1969) found superior dot localization in the right hemisphere in males. However, Buffery and Gray (1972) found girls to be earlier and more fully lateralized on a spatial task and suggested that this may facilitate their verbal development. Since laterality is not as strong or as early in boys, their spatial skills would be facilitated by bilateral representation. Sex differences in cerebral processing of visual tasks have been suspected on the basis of more impaired block designs scored in males with right hemisphere lesions when compared to females (McGlone and Kertesz, 1973). This was interpreted to confirm the previous suggestions that male superiority in spatial tasks results from the greater hemispheric specialization of males. The same study showed no significant difference for aphasia scores (35 males and 22 females). The better performance of normal females on verbal tasks and of the males on visuo-spatial and mathematical tasks is well established in neuropsychology although the actual reason remains debatable; it has been attributed to several factors ranging from different cerebral organization to social causes (*see review* by MacCoby and Jacklin, 1974). Studies of sex differences in dichotic listening show greater laterality effect in men than women (Lake and Bryden, 1976). There is also some morphological sex difference showing more reversal of the typical asymmetry of the planum temporale among females (Wada, Clark and Hamm, 1975). Witelson (1976) found evidence for greater spatial processing in the right hemisphere with a dichaptic task in boys. Interestingly, this is one of the few studies that could not confirm any sex difference for dichotic listening. Females showed left visual field (right hemisphere) superiority in a lexical decision task, suggesting more right hemisphere language function in women (Bradshaw and Gates, 1978). One digit multiplication task showed better performance by women when presented to hemifields with competing stimuli to the opposite hemisphere (Milstein, Small, Malloy and Small, 1979). Right-handed males, however, made more correct responses when the problem was presented to the left hemisphere. Left-handed females with presumed less hemispheric differentiation performed much as did the right-handed males. Males showed more coherence of auditory evoked potentials in the left hemisphere than in the right (Davis and Wada, 1978). Contrary to many other studies, females showed significantly more left hemisphere alpha suppression when listening to verbal material (Moore and Haynes, 1980). The authors implied that the continuous and active nature of the linguistic processing in their paradigm is substantially different from the tachistoscopic and dichotic studies and sufficient to account for the discrepancy.

It appears that sex, handedness, laterality, the modality of presentation and the nature of the task all interact to make the interpretation of the results exceedingly difficult. Some of the controversy is related to the complexity of cerebral function, to the different tasks used, and to the differences between the developing and the mature populations examined. Clinically it appeared to us that there is no significant sex difference in the incidence of aphasia in adults even though some of the hemispheric asymmetries may show sex differences. We decided to address these interdependent issues and examine the sex and age distribution of our aphasics and patients with right hemispheric lesions and compare the language and non-verbal performance of males and females with comparable lesions caused by a recent stroke in a general hospital population.

MATERIAL AND METHODS

Subjects

Aphasia due to stroke. All acute aphasic patients with infarcts consecutively tested between 1969 and 1979 were studied. Referral of aphasics was actively sought from the other hospitals and this sample is considered representative of the acute aphasic population in our community (London, Ontario; population 250,000). Patients from a veterans' hospital were not included to avoid an artificial increase in the number of males in our sample. Few (8) acute patients were lost this way.

We selected 192 who met the following criteria:

1. Ætiology of infarct as diagnosed clinically and radiologically;
2. An initial testing with the Western Aphasia Battery (WAB) within forty-five days post-onset;
3. Mean score for all language tasks on the WAB less than 93.8, which is a cut-off criterion for significant aphasia (Kertesz, 1979);
4. Right-handedness, determined by questioning the patient or a relative about hand-preference for writing, throwing, cutting, drawing, brushing and using a spoon, 4 out of 6 items deciding. Ambidexterity was excluded along with left-handedness;
5. English speaking;
6. Availability of localizing information indicating a single left hemisphere lesion;
7. No previous brain damage.

Of a total of 206 right-handed aphasics with strokes, 114 males and 78 females were found suitable for inclusion in the present study. Five subjects (4 males and 1 female) were excluded because they had had bilateral brain damage, and 5 because there was no localizing information available for them. An additional 4 subjects (1 male and 3 females) were excluded because their aphasia had been caused by right hemisphere lesions ('crossed' aphasia). We only had 6 left-handed or ambidextrous acute aphasics, 5 with left-sided lesions, one with a right-sided lesion, all of whom were excluded. For the majority of patients (99 males and 70 females) the lesions had been localized by a brain scan and/or CT scan. For 10 patients (7 males and 3 females) clinical and EEG information was available and for 12 (8 males and 4 females) the side of lesion was inferred from the presence of right hemiplegia and/or right sensory loss and right hemianopia.

We have obtained the incidence rates of cerebral thrombosis and embolism at St. Joseph's Hospital, London, Ontario, for the decade of 1969–79. The male : female ratio was 216 : 202. Non-hæmorrhagic strokes from Victoria Hospital, London, Ontario, for the year 1974 provided a male : female ratio of 160:119 and for 1975, 192:143. A chi-square analysis of these proportions revealed them to be the same as the male : female ratio of our aphasics ($P = 0.11$, 0.66 and 0.65, respectively). Thus we felt that our sample of male and female aphasics was representative of the population of non-hæmorrhagic strokes.

Right hemisphere strokes without aphasia. Fifty-seven patients with right hemisphere lesion, 40 males and 17 females, with strokes were examined with all the language and non-verbal subtests of the WAB. These patients were recruited as controls and represent all consecutively examined non-dominant hemisphere acute strokes in our laboratory from 1974–79. The criteria for selection were the same as those for the aphasics, except for the side of the lesion and absence of aphasia. It should be noted that the incidence of males to females is higher in this group, which is also smaller than the aphasic group.

Testing and Classification

The Western Aphasia Battery (WAB) (Kertesz and Poole, 1974) had been administered to all subjects. This test is a substantial modification of the Boston Diagnostic Aphasia Examination (Goodglass and Kaplan, 1972). It has been standardized on both aphasic and normal patients, and has been demonstrated to be a valid test of aphasic disability (Kertesz, 1979). The patients were grouped into the eight diagnostic categories of global, Broca's, Wernicke's, conduction, anomic, transcortical motor, transcortical sensory and isolation aphasia. The classification of patients was based on these subtests: (1) spontaneous speech; (2) comprehension; (3) repetition, and (4) naming, according to a synoptic table (Kertesz, 1979). Other subtests such as reading, writing, calculation, praxis, etc. were not used in this classification.

Controlling for Education and Size of Lesion

Education data was available for 86 males and 58 females. The mean number of years of education was 9.51 (SD = 3.23) for the males and 9.93 (SD = 2.81) for the females. A t-test revealed no significant differences between the means ($P = 0.50$).

The lesion size was measured on the CT scan by planimetry as detailed by Kertesz, Harlock and Coates (1979) on 40 male and 30 female aphasics and 18 male and 9 female right hemisphere patients. The lesion sizes were compared by a t-test and no significant differences were found between males and females in the left ($P = 0.2$) or right ($P = 0.1$) hemisphere lesions.

Thus our male and female groups were matched for education and lesion size.

RESULTS

1. *Sex Differences in the Incidence of Aphasia*

The males in our population had a mean age of 64.33 years (SD = 11.24) and the females a mean age of 65.38 years (SD = 14.75). There was no significant difference between the means at $P \leqslant 0.05$ using an unpaired t-test (t = 0.53). Examination of the frequency distributions of ages for each sex revealed that the women formed a wider distribution than the men and that this was also skewed towards the older ages. There were 14 females compared to only 6 males above the age of 80 years. We examined the frequency distribution of male and female ages in the age ranges between 18 and 29, 30 and 39, 40 and 49, 50 and 59, 60 and 69, 70 and 79 and 80 and 95 years using a chi-square analysis (Table 1). The differences in frequency of age occurrence between the sexes were not significant in any age category ($\chi = 12.233$, d.f. = 6, $P = 0.09$) despite the trend towards more women in the oldest age group.

TABLE 1. FREQUENCY DISTRIBUTION OF AGES IN MALE AND FEMALE APHASICS*

Sex	*18–29 y*	*30–39 y*	*40–49 y*	*50–59 y*	*60–69 y*	*70–79 y*	*80–95 y*
Male n = 114	2	2	6	22	41	35	6
Female n = 78	2	4	5	11	19	23	14

* $\chi^2 = 12.233$, d.f. = 6, $P = 0.09$, not significant.

The distribution of sexes among the clinical aphasic types is shown in Table 2. Chi-square analysis revealed that there were no significant differences in the frequency distribution of the numbers of males and females in any type of aphasia ($\chi^2 = 2.014$, d.f. = 7, $P = 0.96$).

2. *Type of Aphasia and Age*

The mean ages for globals, Broca's, Wernicke's conduction and anomic aphasics (Table 3) were analysed by a one-way analysis of variance. The age differences among the groups did not quite reach significance (F = 2.2382, d.f. = 4, 160, $P = 0.067$). However, Broca's aphasics appeared somewhat younger than the globals and Wernicke's when the means were inspected (Table 3). Comparison of the median age of each aphasic group using the median test did not reveal any significant differences either ($P = 0.32$).

3. *Age Groups, Type of Aphasia and Sex Difference*

Using the above age categories and controlling for type of aphasia (global, Broca's, Wernicke's, conduction, anomic, transcortical motor, transcortical sensory, isolation) another chi-square analysis revealed that the distribution of ages

TABLE 2. FREQUENCY DISTRIBUTION OF MALE AND FEMALE CLINICAL APHASIC TYPES*

	Clinical aphasic type							
					Transcortical			
	Global	*Broca*	*Wernicke*	*Conduction*	*Motor*	*Sensory*	*Isolation*	*Anomic*
Male n = 114	23	19	13	12	5	10	1	31
Female n = 78	15	15	10	6	2	6	2	22
Total n = 192	38	34	23	18	7	16	3	53

* $\chi^2 = 2.014$, d.f. = 7, $P = 0.96$, not significant.

TABLE 3. MEAN AND MEDIAN AGES OF APHASIC TYPES

n	*Aphasic type*	*Mean**	*SD*	*Median***
38	Global	66.79	10.4	69.5
34	Broca's	59.03	16.5	62.5
23	Wernicke's	67.74	10.9	67.0
53	Anomic	64.15	13.7	65.5
18	Conduction	66.4	10.5	66.5
7	Transcortical motor	66.6	7.1	66.0
16	Transcortical sensory	66.8	10.9	67.5
3	Isolation	66.3	7.5	66.0
192	Total	66.09		66.5

* One-way ANOVA did not reveal significant differences between the means ($P = 0.067$). ** Median test did not reveal significant differences between the medians ($P > 0.5$).

did not differ significantly for males and females in any type of aphasia. Table 4 summarizes the data including the *P* values. Columns of low frequency representing the age groups below 50 were collapsed for the analysis. A heterogeneity chi-square (Sokal and Rohlf, 1969) was calculated by adding the chi-square values for the distribution of sexes by age for all aphasia types (Table 4) and subtracting from this total the pooled chi-square for the distribution of sexes in the age groups for the whole population (Table 1). This value was not significant ($\chi^2 = 23.38$, d.f. $= 42$, $P > 0.50$) indicating that the various types of aphasia did not differ with respect to age and sex.

TABLE 4. DISTRIBUTION OF AGES CONTROLLING FOR SEX AND TYPE*

		Age intervals (yrs)							
Aphasic Type	*Sex*	18–49	50–59	60–69	70–79	80–95	χ^2	*d.f.*	*P*
Global	M	3	3	5	11	1	2.20	4	0.70
	F	1	2	5	5	2			
Broca's	M	3	4	6	6	0	5.30	4	0.26
	F	5	1	4	3	2			
Wernicke's	M	0	4	5	3	1	4.78	4	0.31
	F	1	1	2	3	3			
Conduction	M	0	4	3	5	0	7.97	4	0.09
	F	1	1	0	2	2			
Transcortical motor	M	0	0	4	1	0	—	—	0.52**
	F	0	0	1	1	0			
Transcortical sensory	M	1	3	2	4	0	2.64	4	0.62
	F	0	1	1	3	1			
Isolation	M	0	1	0	0	0	3.00	2	0.22
	F	1	0	1	0	0			
Anomic	M	3	4	19	6	4	4.46	5	0.49
	F	3	4	7	6	3			

* None of these are significant. ** Calculated using Fisher's exact probability test.

4. *Severity of Aphasia, Language and Non-verbal Performance*

The mean score for each subtest on the WAB was computed for male and female groups, and t-tests did not reveal any significant difference between the sexes. Table 5 summarizes these results. Females tended to perform slightly better than males on the writing subtest. Since our data do not permit us to reject the null hypothesis that there is no difference in language representation in men and women, the probability of missing a small difference in performance between the sexes (type II error) was examined. Based on McGlone's (1977) finding of approximately a 15 per cent difference in verbal IQ between right brain-damaged females and controls, we calculated the power (Tang, 1938) of our methodology for detecting a 15 per cent difference between our male and female samples, and obtained an acceptable 10 per cent probability of committing a type II error. This probability is inversely proportional to the theorized difference between the sexes. Thus, if indeed differences between the sexes do exist, our WAB measures were powerful enough to detect differences of 15 per cent and greater at an acceptable type II error probability.

TABLE 5. MEAN SCORES AND STANDARD DEVIATIONS FOR MALE AND FEMALE APHASICS ON WAB SUBTESTS

	Male		*Female*		
Subtest	*Mean*	*SD*	*Mean*	*SD*	*P**
AQ	48.96	30.98	47.58	32.78	0.77
Fluency	4.98	3.24	4.78	3.68	0.69
Comprehension	11.79	6.03	11.93	6.01	0.88
Repetition	5.20	3.96	5.13	3.99	0.90
Naming	3.93	3.46	3.85	3.58	0.73
Reading	40.15	32.61	40.38	34.42	0.96
Writing	21.13	26.29	26.22	33.81	0.24
Drawing	7.42	9.47	8.14	10.05	0.61
Block design	1.87	6.01	1.54	6.17	0.72
Calculation	9.43	10.65	8.92	10.73	0.75
RCPM	11.58	12.39	11.13	12.22	0.80

* None of these *P* values for t-tests are significant.

5. *Sex Differences, Ages, Language and Non-verbal Scores in Right Hemisphere Lesions*

The ages and the WAB scores of 57 right-handed, right hemisphere-damaged patients were analysed. The mean age of the males (n = 40) was 62.88 (SD = 9.85) and the females (n = 17) was 63.59 (SD = 10.25). A t-test revealed no significant difference between these means at $P \leqslant 0.05$. The distribution of these patients in the decades of 40 to 49, 50 to 59, 60 to 69, and 70–79 years was examined by a chi-square analysis, and again no significant differences between males and females was revealed ($\chi^2 = 0.99$, d.f. = 3, $P = 0.8$).

TABLE 6. MEAN SCORES AND STANDARD DEVIATIONS ON WAB SUBTESTS FOR MALE AND FEMALE RIGHT HEMISPHERE GROUPS

	Male		*Female*		
Subtest	*Mean*	*SD*	*Mean*	*SD*	*P**
AQ	94.55	5.73	95.16	4.93	0.70
Fluency	9.70	0.99	9.71	0.47	0.98
Comprehension	19.12	1.11	19.45	0.76	0.27
Repetition	9.57	0.51	9.76	0.27	0.15
Naming	9.09	0.57	9.04	0.50	0.72
Reading	83.90	18.75	90.24	11.11	0.20
Writing	68.03	23.64	72.94	19.92	0.46
Drawing	14.68	6.10	17.06	4.84	0.16
Block design	3.90	3.35	4.53	3.11	0.51
Calculation	22.25	2.87	22.35	3.18	0.91
RCPM	15.88	9.56	18.00	6.86	0.15

* None of these *P* values for t-tests are significant.

Analysis of mean male and female WAB subtest scores (Table 6) using t-tests showed no significant difference in any subtests although there is a trend for females with right hemisphere lesions to do better on drawing, block design and Raven's Colored Progressive Matrices (RCPM).

DISCUSSION

At first glance, the results suggest that women seem to become aphasic less often than men. This is true if one looks at absolute numbers only. However, when entire stroke populations are examined such as in the review of epidemiological studies by Kurtzke (1976), it becomes evident that the reason for this difference is easily explained by the higher ratio of men suffering strokes. The crude average of the age adjusted rates of 14 studies indicated a male:female ratio of 178:145. Abu-Zeid, Choi and Nelson (1975) identified acute cerebrovascular disease from hospital records in Manitoba in an eighteen-month period. The over-all ratio of infarcts per 100000 population was 108.4 males : 73.9 females. Below the age of 50 years there was no significant sex difference for infarcts. After the age of 50 years the incidence of infarcts rises much higher in men and after 60 years the rate of increase catches up in women also. A community survey of first strokes in Rochester, Minnesota revealed a rate incidence per 100000 of 214 for men and 136 for women (Matsumoto, Whisnant, Kurland and Okazaki, 1973). These ratios vary from 1.07 to 1.57 : 1, with an over-all average of 1.34 : 1. Our ratio of 1.46 : 1 is within the range of these surveys and chi-square analysis of the difference between proportions confirms that it is not significantly different from any of them (all *P* values over 0.1).

It is clear that women become aphasic just as frequently as men when they suffer a stroke in the dominant hemisphere. The lesser incidence of their aphasia is due simply to the lesser incidence of strokes (just like heart attacks) in females especially in the decade between 50 and 60 years (Abu-Zeid *et al.*, 1975). This biological difference has been linked to the protective effect of œstrogen against arteriosclerosis which decreases post-menopausally, accounting for females catching up in the older age groups and even surpassing the males in the incidence of the strokes.

The same biological difference showed up as a trend in the age distribution in our aphasic population. The numbers of males and females were equal in the early decades as their strokes were due to cardiac emboli mostly and not related to arteriosclerosis. In the 50 to 70 years age groups the obvious male preponderance appears but in the eighties, the trend shows a reversal, relating more likely to differences in the age distribution of cerebral arteriosclerosis and possibly to female longevity rather than to cerebral organization of language function. The reversal of the male:female ratio among the elderly aphasics, even though not reaching statistical significance, has to be considered in the context of the total female sample consisting of only about two-thirds as many subjects as the males. Therefore, in order to control for age distribution and to ensure that females were not adversely affected by a possible age by aphasia type or severity interaction, all subjects above the age of 80 years were removed, and the results were recalculated for the remaining population of 108 males and 64 females. There were no significant differences even in this modified population between the sexes concerning age, frequency distribution in decades and types of aphasias.

Assuming that differences in size and location of lesion would be reflected in the clinical classification of aphasics (Kertesz, 1979), the above results indicate that our male and female samples were comparable for both these factors. Planimetric measurements of the lesions on CT as reported above, in fact confirmed this assumption as the male and female lesions were quite comparable in size. The lesion sizes of the left and right hemisphere patients were also compared. A t-test for independent groups revealed no significant differences between the hemispheres either ($P = 0.15$). We were able to match lesion sizes by direct measurement which is an important but often neglected factor when claims are made for significant sex and laterality differences in cerebral organization.

No significant sex differences were revealed in the scores of males and females on the various subtests of the WAB. Females performed somewhat better than males on the writing subtest but this did not reach significance. In the case of more bilateral representation for language in females one would expect that with unilateral damage to the left hemisphere, their language scores would be less impaired relative to males, due to additional language functioning in the right hemisphere. However, our data do not support this notion. In fact, as shown in Table 4, females actually performed slightly worse than males on 4 of the 7 language subtests. Thus our data does not even seem to suggest a trend towards a sparing of language performance in females in left hemisphere lesions, contrary to recently popular beliefs.

The corollary of this is that, given bilateral language representation in women, one would expect right hemisphere-damaged females to have more impairment on language tasks than their male counterparts with similar lesions. This is not supported by our data either (Table 6). On the other hand, previous observations that males with right hemisphere lesions are more impaired in visuo-spatial tasks than females (McGlone and Kertesz, 1973) is confirmed by a trend in sex differences in this population also. We only had 6 sinistrals and ambidextrals among our acute aphasics which is well below the expected incidence of 5 per cent left-handers in the general population. This may be considered to be related to more bilateral language representation in some left-handers sparing them from aphasic disability in case of a lesion on either side. However, it is contrary to the actual increased incidence of aphasia in left-handers in the literature (Hécaen and de Ajuriaguerra, 1964).

There was a difference in the mean age of Broca's and Wernicke's and Broca's and global aphasics among the very old, but the chi-square distribution between the age intervals was not significant. Nevertheless the data confirmed the trend that has been observed by Kertesz and Poole (1974), Brown and Jaffe (1975) and Obler *et al.* (1978). The theoretical explanation for this difference possibly lies in the differing ætiologies of the lesions causing Broca's and Wernicke's aphasia.

The lesions causing infarcts in the frontal and frontoparietal regions may be related more to embolism from cardiac and carotid disease which is more prevalent in the 50 to 70 years age group while parietotemporal infarcts may be the consequence of cerebral thrombosis affecting the posterior branches of the middle cerebral artery more frequently in elderly patients. The distinction between embolism and thrombosis is difficult clinically and pathologically and usually depends on the identification of a source of embolism. More study of the pathology is required to confirm or disprove this hypothesis which is an alternative to the continuing dedifferentiation postulated by Brown and Jaffe (1975).

The distribution of aphasic types in an acute aphasic population such as ours differs significantly from a chronic population which is often the kind examined in rehabilitation clinics or veterans' hospitals. The higher number of Wernicke's and transcortical aphasics is one example. The distribution is also a function of the taxonomy used. We unequivocally classify our patients according to test scores. This avoids the vague and awkward 'mixed' groups. Our relatively large anomic group may contain some of these milder aphasic patients who would appear as 'mixed' in other systems.

SUMMARY

Sex differences and age distribution are examined in various types of aphasia and in right hemisphere-damaged patients due to acute infarct. The language and performance deficits were measured by a standardized test allowing us to group patients meaningfully.

The higher male to female ratio of aphasia is shown to relate to a similar sex distribution in infarcts rather than to sex differences in cerebral organization.

Broca's aphasics were somewhat younger than the other groups and the slight difference may be related to pathophysiological factors favouring embolic strokes in the anterior territory of the middle cerebral artery. Sex and aphasia types were not significantly different in various age groups except above 50 years of age where the female aphasics reversed the ratio.

ACKNOWLEDGEMENTS

We are grateful to Betty Poole, Pat McCabe and Vicki Henderson for collection of data, Chris Young and Alan Donner for statistical advice, to Stan Dobrowolski for comments, and to our colleagues for referring patients. Ontario Health Research Grants PR721 and PR324 supported the work.

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(*Received May 8, 1980*)

Brain (1981), **104**, 129–148

ACUTE VIRAL ENCEPHALITIS
ITS DIAGNOSIS AND OUTCOME

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INTRODUCTION

VIRAL encephalitis is a particularly difficult clinical problem. The diagnosis is not easy to make in the early stages of the disorder since other acute brain disorders, particularly pyogenic brain abscess, cerebral infarction or hæmorrhage, acute multiple sclerosis and tuberculous meningitis may present with similar clinical features. Yet if the best results are to be obtained treatment should be instituted as early as possible. Further, encephalitis may be due to infection with one of several viruses, including influenza group, coxsackie, echo and herpes simplex viruses, or it may follow a viral infection, particularly one of the exanthems—post-infection encephalitis. In addition, in many patients in whom the clinical features and the investigations suggest a diagnosis of viral encephalitis, no direct evidence of viral infection can be found, leaving the cause of the disease in some doubt.

Accurate diagnosis of acute viral encephalitis has become more important since the advent of the possibility of effective treatment for herpes simplex virus encephalitis. Without accurate diagnosis it is not possible to study prognosis and new treatments become difficult to evaluate, both because of the diagnostic uncertainty itself and the resultant unpredictable prognosis.

Previous studies of patients with encephalitis have approached various aspects of the problem. For example, Miller and Ross (1968) reviewed a series of patients suspected of having encephalitis and found that almost 50 per cent had other acute cerebral disorders. Studies on the natural history of encephalitis have largely concentrated on herpes simplex virus (HSV) encephalitis (Johnson, Rosenthal and Lerner, 1972; Williams and Lerner, 1978), or on post-vaccinial (de Vries, 1960) and post-infection encephalitis (Miller, Stanton and Gibbons, 1956; Boughton, 1964). There have been many studies concerned with the investigation of patients with encephalitis; including examination of the CSF (Smith, 1969), serological testing (Miller and Ross, 1968; Lerner, Bailey and Nolan, 1970), electroencephalography (Cobb, 1975) and neuroradiology (Illis and Gostling, 1972; Kaufman, Zimmerman and Leeds, 1979). However, these studies, and those on the outcome

(Miller *et al.*, 1956; Illis and Merry, 1972) and treatment (Miller, 1953; Zeigler, 1966; Longson, 1977) have particularly concerned HSV and post-infection encephalitis.

In this paper we review the clinical features and results of investigation in a retrospective series of 60 patients with virus-related encephalitis admitted to The London Hospital between the years 1963 and 1978. The features of the various types of encephalitis found in these patients are discussed in relation to both diagnosis and outcome.

METHODS

The case notes of all patients coded as having 'encephalitis' admitted to The London Hospital in the fifteen-year period 1963–1978 were reviewed. We have defined acute viral encephalitis as an illness of rapid onset and progression, with signs of diffuse or multifocal involvement of the central nervous system. There is evidence of inflammation of the brain and other causes have been excluded. In most patients the encephalitic illness occurs during or shortly after a viral infection but, in some, the disorder may occur without an associated viral infection. Diagnosis in the latter group is particularly difficult. Patients whose illness did not fulfil these criteria were excluded. For the purposes of this study it was not required that the diagnosis be established by virological proof of viral infection.

RESULTS

There were 60 patients in whom the clinical features and results of investigations were consistent with a diagnosis of viral encephalitis. These consisted of 37 men and 23 women (Table 1).

Three sub-groups emerged:

Group 1 (Proven Acute Viral Encephalitis)

In this group an acute encephalitis was accompanied or preceded by a viral illness. The infecting virus, determined either by culture or by serological methods, was either mumps, influenza A256, infectious mononucleosis or herpes simplex.

Group 2 (Presumed Acute Viral Encephalitis)

The clinical features of the patients in this group were identical to those in Group 1 except that no causative or associated viral infection was recognized.

TABLE 1. SEX INCIDENCE

	Men	*Women*	*Total*
Group 1	9	3	12
Group 2	17	12	29
Group 3	11	8	19

Group 3 (Post-infection Encephalitis)

This group consisted of patients with acute encephalitis in whom a viral-type illness had occurred in the month preceding the onset of the encephalitis. There was an interval of normal health between the two illnesses.

Group 1. Proven Acute Viral Encephalitis

The infecting virus was identified in 12 patients (Table 2). Mumps virus was identified in 2 cases, influenza A256 in one, Epstein Barr virus (infectious mononucleosis) in 3 and herpes simplex virus (HSV) in 6.

Patients with mumps and influenza A256 infections showed a significant rise in serum antibody titre to the appropriate virus. A positive Paul Bunnell test was found in the 3 patients in whom encephalitis was associated with infectious mononucleosis. A diagnosis of HSV encephalitis was made by positive immunofluorescence on brain biopsy material in 3 cases, and by rising titres of HSV antibodies in the CSF in the remaining 3 cases.

TABLE 2. VIRUS TYPE, AGE AND SEX INCIDENCE IN GROUP 1

Virus	*Men*	*Women*	*Total*	*Ages (yrs)*
Mumps	2	0	2	3–39
Influenza A256	1	0	1	57
Infectious mononucleosis	3	0	3	8–39
Herpes simplex	6	3	9	17–76

Clinical features. The 3 patients with mumps or influenza A256 encephalitis all had a prodromal illness of headache with vomiting lasting five to seven days. In the 3 patients with infectious mononucleosis this prodromal illness lasted up to two weeks. In addition the latter had a rash or sore throat, and a generalized lymphadenopathy. The prodromal illness was followed by seizures in 3 patients, disorientation and altered consciousness in 4 and focal neurological signs in 3. Of these 6 patients one died and one had a permanent mild hemiparesis (both had infectious mononucleosis) and the remaining 4 patients made a complete recovery. The following is a typical case history.

Case history 1. This 8-year-old boy presented after two generalized convulsions. He had complained of a cough for two weeks and a sore throat for three days. On admission he was drowsy but there were no focal neurological signs. His temperature was 39° C and there was a generalized lymphadenopathy. The CSF contained 3 lymphocytes and 30 g/l protein. The blood white cell count was 15 500/mm^3 (6 per cent neutrophils, with atypical lymphocytes). A Paul Bunnell test was positive. Five days after admission he complained of headaches, began to vomit and lapsed into a coma. He died that day of respiratory arrest.

The first symptom complained of by 5 of the 6 patients with HSV encephalitis was headache; the other patient presented with dysphasia. All 6 were febrile (38 to 39° C) on admission. One patient presented with visual hallucinations and 2 became confused and disorientated and then dysphasic during their illness. Grand mal seizures occurred in 2 patients and coma developed in 4. The interval between the onset of headache and of coma was four to seven days.

The following is a typical case history.

Case history 2. Five days before admission this 53-year-old woman developed fever and headache. Two days later she became confused and disorientated and developed impairment of memory. On admission she was febrile (38° C) and alert, but dysphasic. Muscular tone was increased on the right and the right plantar response was extensor. The CSF was normal, and the blood white cell count was 13 300/mm^3 (78 per cent neutrophils). The EEG showed bilateral repetitive slow wave complexes seen principally over the temporal regions. On this background there was a little superimposed theta activity. A CT scan showed low attenuation areas in both temporal lobes.

She was treated with adenine arabinoside and dexamethasone but twenty-four hours later she became deeply comatose, and she died eight weeks later. The CSF complement fixation titres for herpes simplex virus antibody rose from 1:64 to 1:1028 over a three-week period.

All our 6 patients with HSV encephalitis were treated with dexamethasone. Two also received cytosine arabinoside or adenine arabinoside. Four patients died, including the 2 treated with these antiviral drugs. These 4 patients became comatose during their illness, but the other 2, who survived, showed only a mild impairment of consciousness during their illness and survived without residual disability.

Laboratory investigations. The CSF was examined in 5 of the 6 patients with mumps, influenza and infectious mononucleosis encephalitis. It was normal in only one case. In the other 4 patients the CSF contained 8 to 341 cells/mm^3. These cells were usually lymphocytes, but in one case 50 per cent of these cells were polymorphs. The CSF protein was raised in only 2 cases.

The CSF contained more than 100 cells/mm^3 (range 130 to 300) in 5 of the 6 patients with HSV encephalitis. These cells were either predominantly polymorphs (2 cases) or lymphocytes (4 cases). The CSF protein was normal in 2 cases and was between 40 and 100 g/l in the others. The CSF glucose was normal in all cases.

Apart from the finding of atypical lymphocytes in the blood of all the patients with infectious mononucleosis the blood white cell count was raised in only 3 patients.

Electroencephalography (EEG). The EEG was recorded in each of these 12 patients. It was abnormal in all those with mumps, influenza and infectious mononucleosis encephalitis, showing diffuse slowing of activity in 3 patients, localized slowing in 2, and bursts of spike and wave activity in one patient.

The initial EEG in each of the 6 patients with HSV encephalitis was abnormal, showing marked bilateral slowing of background activity with focal accentuation in 3 cases. Repetitive slow wave complexes (Upton and Gumpert, 1970) were seen in the initial EEG in 3 patients and developed after two days in one patient. All 4 patients with this feature died.

Radiological investigations. In HSV encephalitis the CT scan was normal in one patient, but showed areas of decreased attenuation in the temporal lobes of one patient and in the left parietal lobe in another. Carotid angiography was performed in the remaining 3 patients; it was normal in 2 but in the other there was swelling of the left temporal lobe.

CT scans were performed in only 2 of the remaining 6 patients in Group 1. In both no abnormality was found.

Group 2. Presumed Acute Viral Encephalitis

Our clinical criteria for the diagnosis of acute encephalitis, due to an unidentified virus, were satisfied in 29 patients in whom no direct virological proof of infection was obtained. There were 17 males, aged 3 to 66 years, and 12 females, aged 4 to 51 years (Table 3). There was a predilection for the disease to present in autumn and early spring (Table 4).

TABLE 3. AGE STRUCTURE IN GROUP 2

Age (yrs)	< 10	10–19	20–29	30–39	40–49	50–59	60–69	> 70	*Total*
Cases	7	6	5	4	3	2	2	0	29

TABLE 4. SEASONAL INCIDENCE IN GROUP 2

Month	*Jan.*	*Feb.*	*Mar.*	*Apr.*	*May*	*June*	*July*	*Aug.*	*Sept.*	*Oct.*	*Nov.*	*Dec.*
Cases	1	2	5	0	2	2	3	3	1	4	5	1

Clinical features. The presenting symptoms and signs of these patients are shown in Table 5. Headache (62 per cent), vomiting (41 per cent) and fever (41 per cent) were frequent. Drowsiness was a feature in 34 per cent of these patients, 28 per cent were in coma on admission. A further 7 became comatose during the course of their illness so that coma was a feature in 52 per cent. Focal or generalized seizures occurred after the development of headache, fever and drowsiness in 38 per cent of cases. The commonest focal sign was hemiparesis, which was found in half the patients.

The following are typical case histories of a mild (Case 3), and of a fatal (Case 4) illness, respectively.

Case history 3. This 24-year-old man was febrile and complained of headaches for six days before presenting with drowsiness of a day's duration followed by two grand mal convulsions. On admission he was drowsy with bilateral extensor plantar responses. There was no fever and there were no signs of meningism. After admission he had several right-sided focal seizures. The CSF contained 42 lymphocytes/mm^3 and 10 g/l protein. The blood white cell count was normal. An EEG showed a generalized abnormality with irregular slow activity over the left hemisphere. A CT scan was normal. He was treated with anticonvulsant drugs and recovered completely in two weeks. Repeated serum viral antibody studies showed no change in titre to a standard battery of serological tests.

Case history 4. This 51-year-old woman complained of feeling generally unwell, and of headache and nausea for three days before admission. She was admitted after a brief episode of slurred speech with tingling in the right hand. She was drowsy but apyrexial, and there was no stiffness of the neck. There was a mild right hemiparesis. During the next twelve hours she became deeply comatose and had apnœic attacks. The CSF contained 8 cells/mm^3 (50 per cent lymphocytes, 50 per cent polymorphs) and 15 g/l protein. Her blood white cell count was normal. The EEG showed widespread theta and delta waves and the CT scan showed some low attenuation areas in the frontal regions. A brain biopsy showed a mild degree of œdema and cytotoxic neuronal change. There was some microglial proliferation and occasional mononuclear cells were seen. Immunofluorescent stains of frozen sections for HSV antigen were negative and electron microscopy failed to reveal virus particles. Two days after admission the complement fixing antibody titres to HSV were 1:128, to measles were 1:64 and to influenza A were 1:32. Despite the negative fluorescent studies it was thought that she had HSV encephalitis and she was treated with dexamethasone, mannitol and adenine arabinoside but she deteriorated and died three days later.

The over-all mortality in this group of patients was 10 per cent (n = 3) and the morbidity 28 per cent (n = 8). The latter included hemiparesis, bulbar palsy and

TABLE 5. PRESENTING SYMPTOMS AND SIGNS IN GROUP 2 (29 CASES)

	No. of cases	%
Headache	18	62
Hemiplegia	14	48
Fever	12	41
Nausea/vomiting	12	41
Drowsiness	10	34
Coma	8	28
Neck stiffness	7	24
Papillœdema	7	24
Generalized seizure	6	21
Nystagmus	6	21
Ataxia	6	21
Mental change	5	17
Focal seizure	5	17
Anisocoria	5	17
Dysphasia	2	7
Diplopia	2	7
Dysarthria	1	3
Hemianopia	1	3

epilepsy. Twenty patients were treated with anticonvulsant drugs and with antibiotics in the short period before exclusion of a bacterial infection. Of these, 16 made a complete recovery and 4 had a mild neurological deficit. Nine patients treated with dexamethasone, who were seriously ill on admission, fared less well. Of these only 2 recovered fully and 3 died. The 4 other survivors showed minor or moderate neurological disability.

TABLE 6. CSF CONSTITUENTS IN GROUPS 2 AND 3

A. *White blood cells* (No./mm^3)

	< 4	4–19	20–49	50–99	100–200	> 200
Group 2 (n = 26)	9	5	4	6	1	1
Group 3 (n = 19)	6	6	2	2	2	1

B. *Protein* (g/l)

	< 40	40–99	> 99
Group 2	14	11	1
Group 3	8	10	1

Laboratory investigations. The CSF was examined in 26 of the 29 patients in this group. The CSF was normal in 8 (31 per cent) patients and the findings in the remaining 18 cases are shown in Table 6.

The cell count was raised in all but 9 cases. In 75 per cent the CSF cellular response consisted of more than 75 per cent lymphocytes. The CSF protein was raised in 12 (60 per cent) patients (Table 6B). The CSF sugar was normal in all the patients in whom it was measured.

The blood white cell count was raised (greater than 11 000/mm^3) in 9 of 26 patients. It was greater than 18 000/mm^3 in only 2 patients; a lymphocytosis was found in only 3 patients, 2 of whom had normal total counts.

Standard serological tests for herpes simplex, varicella, mumps, measles, influenza A and mycoplasma pneumoniæ antibodies were performed on admission and three weeks later in 21 patients. No patient in this group had a significant rise in these titres during the illness.

Electroencephalography. An EEG was recorded in 27 patients. It was normal in 3 and showed an abnormal spike and wave focus in another 3. The commonest abnormality, bilateral delta or theta waves, was found in 15 patients; a further 6 showed a unilateral predominance.

Radiological investigations. Nineteen patients had neuroradiological investigation. Ten patients had carotid angiograms, 9 had air encephalograms and 9 had CT scans. Abnormalities were found in only 5 cases. In one an AEG showed

TABLE 7. AGE INCIDENCE IN GROUP 3

Age (yrs)	< 10	10–19	20–29	30–39	40–49	50–59	60–69	> 70	*Total*
Cases	2	4	5	1	5	0	2	0	19

cortical atrophy, in another, carotid angiography showed evidence of a left temporal mass lesion and in 3 the CT scan was abnormal. Two CT scans showed cerebral œdema and the other showed an area of low attenuation in the inferomedial aspect of the left temporal lobe which had resolved three weeks later.

Group 3. Post-infection Encephalitis

Nineteen patients satisfied the clinical criteria for post-infection encephalitis. There were 11 men aged 14 to 69 years and 8 women aged 3 to 42 years (Table 7). Eighteen of these 19 cases occurred during the seven winter months of October to April.

Prodromal illness. The symptoms of the prodromal illness are shown in Table 8. One case followed a smallpox vaccination, and 3 followed an exanthem. One of the latter was thought to be due to measles but the other 2 had non-specific erythematous rashes. In the remaining 15 patients the preceding illness consisted of malaise, myalgia and fever, sometimes associated with nasal congestion.

The interval between the prodromal illness and encephalitis was always more than four days (Table 9); it was less than eleven days in 68 per cent of the patients.

Clinical features of the encephalitic illness. The various symptoms and signs found on admission in the 19 patients are shown in Table 10. Eight (42 per cent) were febrile (usually < 39.5° C). Six were drowsy and a further 3 were comatose. Only another 2 patients became comatose after admission. Altered consciousness, therefore, was a feature of 47 per cent of patients in this group at presentation.

TABLE 8. SYMPTOMS OF ANTECEDENT ILLNESS IN GROUP 3

	No. of cases	%
Fever	11	58
'Flu'	9	47
Headache	6	32
Sore throat	5	26
Cough	5	26
Nasal congestion	4	21
Rash	3	16
Vomiting	2	11

TABLE 9. INTERVAL BETWEEN ANTECEDENT ILLNESS AND ONSET OF ENCEPHALITIS IN GROUP 3

Days	*No. of cases*	%
0–3	0	0
4–6	5	26
7–10	8	42
11–15	3	16
15–30	3	16

The next commonest presenting symptom was a generalized seizure which occurred in 7 cases (37 per cent). The commonest focal sign was a hemiparesis which occurred in 11 cases (58 per cent).

The following are typical case histories.

Case history 5. This 14-year-old boy developed a rash and sore throat which resolved spontaneously after three days. It was not associated with fever. Six days later he developed headaches, sore throat, fever and vomiting and was admitted to hospital. There were no focal signs on admission and it was thought that he had bacterial meningitis. The CSF contained 177 white cells/mm^3 (65 per cent lymphocytes) and 70 g/l protein. The CSF sugar was normal. The blood white cell count was 19300/mm^3 (84 per cent neutrophils). He was treated at first with penicillin and chloramphenicol but the CSF proved sterile and the antibiotics were stopped. He improved in the forty-eight hours after admission.

TABLE 10. PRESENTING SYMPTOMS AND SIGNS IN GROUP 3 (19 CASES)

	No. of cases	%
Hemiplegia	11	58
Fever	8	42
Generalized seizure	7	37
Neck stiffness	6	32
Drowsiness	6	32
Nystagmus	6	32
Quadriplegia	4	21
Papillœdema	4	21
Aniscoria	4	21
Headache	3	16
Coma	3	16
Hemi-anæsthesiæ	3	16
Mental change	2	11
Ataxia	2	11
Nausea/vomiting	1	5
Dysphasia	1	5
Diplopia	1	5
Dysarthria	1	5
Hemianopia	1	5
Focal seizure	0	0

Eight days after admission he complained of diplopia and became confused and febrile. At this time he was found to be drowsy with marked dysarthria, nystagmus sustained in all directions, a left upper motor neuron facial weakness, absence of the gag reflex and poor palatal movement. There was a mild left hemiplegia with ataxia in all four limbs, and both plantar responses were extensor. The CSF contained 10 lymphocytes/mm^3 and 10 g/l protein. An EEG showed bilateral slowing of background elements with focal disturbance. The CT scan was normal. A diagnosis of post-infection encephalitis was made and he was started on dexamethasone. He gradually improved and after two weeks the only abnormal signs were nystagmus on gaze to the left and a minimal ataxia of the upper limbs. Two weeks later these abnormalities had resolved.

Case history 6. This 40-year-old woman became confused, disorientated in space and then increasingly drowsy four days after recovery from a brief, viral-type illness consisting of headache, myalgia and fever. On admission, there was dysphasia, a right hemiparesis and bilateral papillœdema. Her temperature was normal.

A CT scan showed low attenuation areas in both frontal lobes and the EEG showed bilateral theta and delta waves. The blood white cell count was 14700/mm^3 (82 per cent neutrophils) and the CSF was normal. She was treated with dexamethasone and, because a diagnosis of HSV encephalitis was considered likely, adenine arabinoside was also commenced. A brain biopsy from the left frontal lobe was negative for HSV antigen with immunofluorescent staining. Microscopy of the biopsy showed vacuolar neuronal change with perivascular lymphocytic infiltration. During the next twenty-four hours she became deeply comatose and developed bilateral decerebrate postures. She remained in this state for several days, remaining comatose for a further three weeks. There was a slow improvement and six weeks later she was alert but disorientated, and able to walk only with assistance. She had a profound impairment of short-term memory with dressing apraxia and a dense right homonymous hemianopia. When reviewed more than a year after the illness there had been no further improvement.

The over-all mortality in this group of patients was 5 per cent ($n = 1$) and the morbidity 42 per cent ($n = 8$). Thus 11 patients had no residual disability when seen three months after their illness. Of the 8 patients with residual disability, half were sufficiently mildly affected to enable them to lead independent and useful lives. The 5 patients who were comatose during their illness had some residual neurological disability. Three of these patients had been treated with dexamethasone. Of the other 6 patients treated with dexamethasone one died and 2 had neurological deficits, the other 3 making a full recovery.

Laboratory investigations. The CSF was completely normal in only one of the 19 patients in this group (Table 6). Of the remaining 18 patients, the CSF protein was raised in 11 and in all but one it was less than 100 g/l. The cellular constituents were normal (< 4 cells/mm^3) in 6 patients and in only 3 patients were there more than 100 cells/mm^3. In 10 of the remaining 13 patients with raised cell counts, the lymphocyte count was greater than 75 per cent. In 2 patients there were between 50 and 75 per cent lymphocytes, in one 60 per cent polymorphs (total count 47 cells/mm^3), and finally one patient had 100 per cent polymorphs (total cell count 50 cells/mm^3). In 6 of the 18 patients the CSF protein was normal but the cell count was raised, and in 4 patients the reverse was true. Thus 8 patients had both a raised protein level and a raised cell count.

The blood white cell count was available in 18 patients. In 10 patients it was above 11 000/mm^3, being above 16 000/mm^3 in only 2 patients. The differential count was normal in all patients.

Serological tests for viral antibodies were negative in the 11 patients in whom these tests were performed.

Electroencephalography. An EEG was recorded in 18 patients and abnormalities were found in 16. Bilateral slow waves (theta or delta) were noted in 13 patients and unilateral slow wave abnormalities in 3.

Radiological investigations. Neuroradiological investigation was performed in 10 patients. Five had carotid angiography. In one of these ventricular enlargement was found and in the other there was bowing of the pericallossal vessels. Four lumbar or ventricular air encephalograms were performed, 2 of which showed dilated ventricles.

Five patients had CT scans. Two showed decreased attenuation in the frontal or temporal lobes, respectively. Cerebral œdema was noted in 2 other patients.

Pathology

Brain tissue was obtained for microscopical examination in 11 patients, by biopsy in 8 and at autopsy in 3. Four were from Group 1; three of these were cases of HSV encephalitis and the other was a patient with infectious mononucleosis. This case was previously reported by Sworn and Urich (1972). Three were from Group 2 and 4 from Group 3. Each specimen was rated as showing mild, moderate or severe changes in relation to the following features: cerebral œdema, cytotoxic neuronal change, perivascular and generalized mononuclear cell infiltration, microglial proliferation and perivascular demyelination. The results are summarized in Table 11.

TABLE 11. PATHOLOGICAL FINDINGS

	Case	*Age*	*Sex*	*PM B*	*Œdema*	*Cytotoxic neuronal change*	*Generalized mononuclear cell infiltration*	*Perivascular mononuclear cell infiltration*	*Microglial proliferation*	*Perivascular demyelination*
Group 1	1	65	M	B	+++	++	+	0	++	0
	2	17	F	B	++	+++	++	+++	++	0
	3	76	F	PM	+++	+++	++	+++	+++	0
	4	13	M	B	0	++	++	+	++	0
Group 2	5	24	F	B	+	+	++	0	++	0
	6	51	F	B	+	+	+	0	+	0
	7	9	M	B	++	++	+	+	++	No WM
Group 3	8	40	F	B	++	+	0	+	+	+
	9	15	M	B	+	+	0	++	+	0
	10	8	M	PM	0	++	0	+++	++	No WM
	11	20	F	PM	0	+	0	++	+	++

Case 1–3, herpes simplex virus. Case 4, infectious mononucleosis. PM = post-mortem. B = brain biopsy. WM = white matter. + = mild ++ = moderate. +++ = severe.

The most marked abnormalities were seen in patients with HSV encephalitis. These included œdema, cytotoxic neuronal changes, microglial proliferation and perivascular cellular infiltration. The patients in Group 2 showed similar changes to those in HSV encephalitis but they were less severe. Perivascular demyelination was found only in those patients with post-infection encephalitis. In 2 patients, one in Group 2 and one in Group 3, brain biopsies did not include white matter, but were restricted to cortical grey matter and in these the presence or absence of demyelination could not be assessed.

DISCUSSION

The term 'viral encephalitis' is difficult to define. It includes various clinical syndromes, varying from a mild illness of short duration to a fulminant disorder leading to coma and death. A clinical diagnosis of viral encephalitis is often difficult to make, and other disorders must be excluded (Miller and Ross, 1968).

Clinical evidence of an inflammatory brain disorder is an important clue to the diagnosis of acute viral encephalitis, and this was present in most of our patients. Fever was a feature in 50 per cent of the patients with encephalitis in whom a virus was isolated (Group 1), or who had a similar illness without direct proof of viral infection (Group 2), and in 25 per cent of patients with post-infection encephalitis (Group 3). Neck stiffness was found in 25 per cent of the whole group of patients, and signs of brain disease, consisting of clouding of consciousness or focal abnormalities, were present in all of them. The CSF was abnormal in 85 per cent, and the EEG in 90 per cent of our cases.

In the patients in Group 1, in whom encephalitis was associated with an identified viral infection, there were few clinical features which enabled a distinction between the various types of viral infection to be drawn. Headache and vomiting were prominent features in the prodromal phase of HSV encephalitis but these symptoms also occurred in more than half the patients with mumps, influenza, infectious mononucleosis (Group 1) or presumed viral encephalitis (Group 2). Further, headache and vomiting occurred in a similar proportion of patients who became comatose during their illness, in whom the prognosis was poor, as in those who did not become comatose.

Patients with post-infection encephalitis (Group 3) had a different presentation. Most of these patients presented with clinical signs of an acute neurological disorder, for example, a generalized seizure, altered consciousness or hemiparesis. Fever, vomiting and headache were less common features. The diagnosis was often suggested by a history of an infection of viral type in the preceding few days, from which recovery had occurred before the cerebral illness began. Despite these distinctions, in most of our patients the clinical features were insufficiently characteristic to enable a definite diagnosis of acute viral encephalitis to be made without investigation.

Examination of the CSF is commonly carried out in patients with encephalitis, and 56 of our 60 patients had a lumbar puncture. The presence of a lymphocytic cellular response is widely regarded as an important diagnostic feature of viral encephalitis (Illis, 1977). However, the CSF was normal in 25 per cent of our patients in Group 2, and in one patient in Group 1. In 2 patients with HSV encephalitis there was a predominantly polymorphonuclear pleocytosis in the CSF, an observation which has been noted previously (Sarrubbi, Sparling, and Glezen, 1973). There was a lymphocytic response in almost all the patients with post-infection encephalitis (Table 6).

The CSF findings in patients with cerebral abscess may be similar to those of viral encephalitis; for example, Smith (1969) noted that in 70 per cent of patients with cerebral abscess the CSF showed a predominance of lymphocytes, the cell count varying from 6 to $50/mm^3$. The CSF protein in our patients with encephalitis was rarely greater than 100 g/l, a finding also similar to that of brain abscess. A further point of difficulty in interpreting CSF findings is that the CSF glucose may sometimes be reduced in HSV encephalitis (Jacoby, Blennerhasset and Richardson, 1971). The CSF results in our patients were of no value in predicting prognosis in any of the three groups.

The white cell count in venous blood was raised in 55 per cent of patients with post-infection encephalitis and showed typical abnormalities in the patients with infectious mononucleosis, but was normal in the other patients. In the extreme form of post-infection encephalitis, acute hæmorrhagic leucoencephalitis, the blood white cell count is invariably raised (Behan, Moore and Lamarche, 1973).

The use of serological tests to determine the causative virus in patients with encephalitis is often unrewarding (Miller and Ross, 1968). In our patients with the clinical syndrome of acute primary viral encephalitis (Groups 1 and 2) the causative virus was determined by serological tests in only 32 per cent of patients. The clinical features and outcome in the patients in whom these tests were negative (Group 2) were similar to those of the patients in Group 1.

The absence of proof of virus infection in the patients in Group 2 may reflect the limited screening tests for virological infections routinely performed at The London Hospital. For example, tests for coxsackie infections are never carried out although coxsackie B5 virus has been known to cause encephalitis in Essex (Heathfield, Pilsworth, Wall and Corsellis, 1967). Virological diagnosis remains unsatisfactory both because of the wide range of viruses that must be tested, and because of the inevitable delay, usually nearly a month, before the results of changing complement fixing titres become available.

The EEG was of considerable value in patients with acute viral encephalitis (Groups 1 and 2) in as much as it provided evidence of generalized cerebral disorder in the majority of cases, even when there were only minor clinical abnormalities. This was usually shown by diffuse bilateral slowing in the delta and theta frequencies. However, the EEG was only of value in individual patients in relation to the diagnosis of HSV encephalitis. Within our groups of patients with encephalitis periodic complexes, including sharp waves and slow waves in the temporal leads (Upton and Gumpert, 1970) were found in 4 of the 6 patients with HSV encephalitis, but in none of the other patients. Illis and Taylor (1972), however, noted similar EEG changes in cerebral infarction, raised intracranial pressure and other conditions. This EEG abnormality would be particularly useful if it were present during the early stages of HSV encephalitis, but on this point the literature is not clear. Periodic complexes can occur as early as the third day of the illness although they more usually occur during the second week, at the height of the illness. Although Ch'ien, Boehm, Robinson, Liu and Frenkel (1977) recently claimed that EEG abnormalities were of value in the early diagnosis of HSV encephalitis, all their patients were comatose and all died. All our patients with periodic complexes also died. However, this correlation is not absolute in other series (Illis and Taylor, 1972). In post-infection encephalitis, the EEG may be useful as an index of persistence of the disorder (Ziegler, 1966), or of relapse (Durston and Milnes, 1970).

Neuroradiological investigations were carried out in some of our patients to exclude other disorders. Computerized tomographic (CT) scanning was available in 30 per cent of our patients but the yield of abnormalities was low. In 2 of the 3 patients with HSV encephalitis in whom a CT scan was performed zones of decreased attenuation were found in one temporal lobe in one case, and in a parietal lobe of the other.

CT scanning in the 17 patients with HSV encephalitis described by Davis, Davis, Kleinman, Kirchner and Taveras, (1978) and Kaufman *et al.* (1979) showed abnormalities in every case. Some of these were present early in the illness, before the onset of coma. CT scanning of patients with post-infection encephalitis showed evidence of cerebral œdema, but no other distinctive pattern emerged. Two patients had areas of decreased attenuation in their cerebral hemispheres, a finding previously described in acute hæmorrhagic leucoencephalitis (Reich, Lin and Goldblatt, 1979). Enhancing periventricular lesions, as in patients with acute multiple sclerosis (Harding, Radue and Whiteley, 1978), were not found in any of our patients.

A diagnosis of acute viral encephalitis is usually made on the clinical features and results of investigations, but histological evidence is required to confirm this diagnosis. Brain biopsies or autopsy findings were available in 11 (18 per cent) of our cases, including patients in each of the three groups. The clinical features of these patients were similar to others not studied by biopsy or an autopsy. In Groups 1 and 2 the typical features of encephalitis due to direct viral invasion were found. There was neuronal destruction with infiltration of the Virchow-Robin spaces (Greenfield, 1930) and inclusion bodies were sometimes seen. These abnormalities were most marked in those patients with HSV encephalitis (Table 11). The similarity of the pathological findings in patients in Groups 1 and 2 support our suggestion that all these patients had viral encephalitis, despite the absence of virological proof of this diagnosis in the patients in Group 2.

Four patients with post-infection encephalitis (Group 3) showed evidence of perivascular infiltration and 2 also showed demyelination, the two typical features of this condition (Ferraro and Roizin, 1957). The biopsy from one of these patients did not include white matter. Without assessment of the underlying white matter for perivascular demyelination brain biopsy is of limited value in the differential diagnosis of encephalitis, since post-infection encephalitis cannot be recognized.

The post-mortem findings in one patient, in whom a clinical diagnosis of post-infection encephalitis was made, illustrate a problem in the nosology of this condition.

Case history 7. A 20-year-old woman developed an influenza-like illness, with fever, myalgia and headache, which persisted for five days. Two weeks later she noticed numbness of her left leg which spread in a few days to the right lower costal margin. Ten days later she developed headache and vomiting and during the next five days a progressive opthalmoplegia with bilateral facial weakness, a right palatal palsy and a left hemiparesis developed. Both plantar responses were extensor.

A CT scan showed small ventricles, but no other abnormality. The EEG showed bilateral posterior delta waves, more marked on the right than the left, with bursts of bifrontal synchronous delta activity.

A diagnosis of post-infection encephalitis was made and dexamethasone was begun. However, she became increasingly drowsy and the opthalmoplegia became complete. A second CT scan showed irregular, non-enhancing areas of low attenuation on both temporal lobes. There was no improvement and she died of septicæmia five weeks later.

At autopsy the brain was œdematous and several large, fresh demyelinating lesions were seen in the corpus callosum, frontal white matter, and brain-stem. Histologically, there was extensive demyelination in the subcortical white matter, and in the brain-stem and cerebellum. In addition, there was swelling, irregularity and loss of axons in these areas. Several thick cuffs of lymphocytes and mononuclear cells were seen around vessels in the most recent lesions, but perivascular cellular infiltration was sparse elsewhere in the brain. These findings were thought to be consistent with a diagnosis either of post-infection encephalitis or of acute multiple sclerosis of the Marburg type.

This patient exemplifies the problem of differentiating post-infection encephalitis and acute multiple sclerosis. McAlpine (1931) suggested that the following points were in favour of acute post-infection encephalitis; a fever over 100° F, shooting pains, absence of deep reflexes in the lower limbs, and drowsiness or coma. Diplopia, retrobulbar neuritis particularly if unilateral, and sensory loss involving postural and vibration sense are suggestive of multiple sclerosis. It is often only subsequent events, however, which provide a resolution to this dilemma. Thus 4 of van Bogaert's (1950) 19 patients, and 5 of Miller and Evans (1953) 34 patients with acute disseminated encephalomyelitis had recurrences of their illness, observations more suggestive of multiple sclerosis. However, Ziegler (1966) and Durston and Milnes (1970) have also suggested that post-infection encephalomyelitis may pursue a relapsing course.

Outcome

It is generally considered that HSV is the main cause of sporadic fatal viral encephalitis (Meyer, Johnson, Crawford, Dascomb and Rogers, 1960; Whitley, Soong, Dolin, Galasso, Ch'ien and Alford, 1977): indeed, in our small series the mortality was 67 per cent. In different reports the mortality of untreated HSV encephalitis varies from 50 to 70 per cent (Illis and Merry, 1972; Longson and Bailey, 1977). However, in the 35 patients in our Groups 1 and 2 with acute primary viral encephalitis of known or undetermined ætiology, but excluding HSV encephalitis, the mortality was 12 per cent and the morbidity 26 per cent. Comparable figures from the literature are not available, but our experience reflects a considerable mortality and morbidity in the group of patients in whom the virus presumed responsible for the illness was not determined. More effective virological studies are required if progress is to be made in understanding and treating these patients.

Treatment of acute primary viral encephalitis has largely concentrated on patients with HSV encephalitis. It has been suggested that the neurological deficit in HSV encephalitis is due not so much to viral replication, giving rise to cytotoxic neuronal change, but to the severe virus-induced immuno-inflammatory response resulting from the host's immune reaction. The latter leads to cerebral œdema and compression, and to infarction and death (Illis and Merry, 1972; Habel and Brown, 1972; Illis and Gostling, 1972). This concept suggests that steroids should lead to improvement and Illis and Merry (1972), in an analysis of all reported cases of HSV encephalitis, concluded that the mortality was reduced from 70 to 44 per cent with steroid treatment. In our six patients, however, dexamethasone (16 mg/day) appeared to have little effect.

The prognosis of post-infection encephalitis must also be considered. Post-infection encephalitis or encephalomyelitis occurring in relation to immunization and to the exanthems is well known (Miller *et al.*, 1956; de Vries, 1960; McNair Scott, 1967; Behan and Currie, 1978), but few cases have been reported (Turnbull and McIntosh, 1926; Greenfield, 1930, 1955; Crome, 1954; Flewett and Hoult, 1958) following an influenzal or upper respiratory tract infection. However, 80 per cent of our patients with this syndrome developed it after such an infection. The most frequent and most serious of the post-exanthem encephalitides is that due to measles. In two large series of cases reviewed by Miller *et al.* (1956) and by Boughton (1964) there was a mortality of 22 per cent and 9 per cent, respectively, and residual neurological deficits were present in 34 per cent and 23 per cent cases, respectively. Convulsions and coma were the worst prognostic signs, although the duration of coma was not important. Encephalitis following rubella, mumps, and chicken pox has a mortality of about 8.5, 33 and 16 per cent and a morbidity of 20, 22 and 10 per cent, respectively, (Miller *et al.*, 1956).

There was only one death (5 per cent) in our 19 patients with post-infection encephalitis; indeed this patient (Case history 7) may have suffered from acute multiple sclerosis rather than post-infection encephalitis. The morbidity of 44 per cent in our patients, however, is unexpectedly high. There is no comparable study of a large group of patients with encephalitis associated with an unspecified, antecedent infection, presumed to be viral in type, but during the epidemic of Asian influenza in 1957—1958 there were several reports of post-infection encephalitis. Of the seven patients reported by Flewett and Hoult (1958) and McConkey and Daws (1958), none died and the morbidity was only 14 per cent.

The mortality and morbidity in our patients with post-infection encephalitis was related to the extent of the neurological deficit found during the illness. All five patients who were in coma during the illness had some degree of residual neurological deficit and those with marked neurological signs during their illness were more likely to have residual disabilities.

Steroid therapy in post-infection encephalitis has never been evaluated in a controlled study, although it has been suggested that this treatment is helpful (Miller, 1953; Selling and Meilman, 1955; Ziegler, 1966). In our patients, steroids did not seem to reduce morbidity. The degree of neurological disability found at the height of the illness was roughly comparable in the treated and untreated groups; 50 per cent of the former and 88 per cent of the latter were free of residual deficits following the illness. However, cases which were steroid-responsive have been described, for example, the two cases of Ziegler (1966) in which relapse occurred on reducing the dose.

Finally, although acute primary viral encephalitis (Groups 1 and 2) and post-infection encephalitis (Group 3) have been considered separately in this analysis, we consider that these disorders are related problems. Indeed, there is evidence that the two disorders may coexist. For example, Koenig, Rabinowitz, Day and Miller (1979) described a patient with HSV encephalitis who recovered following treatment with adenine arabinoside but developed a second phase of the illness, characterized by an unrelenting post-immune reaction and the appearance of a post-infection encephalitis. Part of the similarity of the clinical features of primary viral and post-infection encephalitis may relate to the possibility that the brain lesion in both groups may result from damage induced by the immune response itself, rather than to the effects of viral invasion alone. The causative agent itself may thus be of less importance than the immune reaction induced in the central nervous system. Reik (1980) has recently reviewed this concept, which adds further weight to the suggestion that treatment of patients with acute primary viral encephalitis should include both immunosuppressive and, when appropriate, antiviral drugs.

SUMMARY

Sixty patients with acute viral encephalitis admitted to The London Hospital in the last fifteen years have been reviewed. These consisted of 12 patients with known viral infection, 29 patients with acute viral infection of undetermined type, and 19 patients in whom an encephalitic illness followed a viral infection (post-infection encephalitis).

The patients with primary viral encephalitis presented with an inflammatory brain disorder, including headaches and fever, and developed focal or diffuse

neurological signs. Patients with post-infection encephalitis, usually following a 'flu'-like illness, presented with an acute neurological disturbance. The results of investigations, including virological studies, CSF examination, electroencephalography and neuroradiology, are described. Biopsy or autopsy material was available in 11 patients and these pathological findings supported the clinical classification of these patients.

The mortality was highest in patients with herpes simplex virus encephalitis and lowest in patients with post-infection encephalitis. A considerable morbidity was found, not only in patients with primary viral encephalitis, but also in patients with encephalitis of unknown ætiology and post-infection encephalitis.

ACKNOWLEDGEMENTS

We are grateful to Dr C. Scholtz for his help in examination of the pathological material, and to our colleagues in the Section of Neurological Sciences of The London Hospital for permission to study their patients.

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(*Received May 27, 1980*)

Brain (1981), **104**, 149-166

CEREBRAL POTENTIALS EVOKED BY MUSCLE STRETCH IN MAN

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INTRODUCTION

THERE has been a great deal of recent interest in long-loop stretch reflexes (Phillips, 1969; Evarts, 1973; Marsden, Merton and Morton, 1973; *cf.* Desmedt, 1978, for review) and kinæsthetic sense (*cf.* McCloskey, 1978), both of which are believed to involve the activity of muscle spindle endings, but little is known about the projection of spindle afferents to the cerebral hemispheres in man. Cerebral potentials preceding and following voluntary movement have been the subject of extensive analysis (Kornhuber and Deecke, 1965; *cf.* Desmedt, 1977, for references), but in these studies the potentials associated with passive movement have been studied only in passing, as a necessary experimental control. Passive movement of the index finger can induce a cerebral potential, but this has been demonstrated to be predominantly of cutaneous origin (Papakostopoulos, Cooper and Crow, 1974, 1975). Cerebral potentials have been induced by percussion of the Achilles tendon (Laffont, Bruneau, Jusseaume, Lelord and Bretonneau, 1975), but the emphasis of this study was to define the cerebral potentials associated with the reflex contraction of triceps suræ rather than the potentials resulting from the percussion-induced afferent volley.

The present study was undertaken to define in normal man the somatosensory cerebral potential evoked by passive plantar flexion movements of the ankle joint with a view to determining whether this potential results from the activity of muscle spindle endings.

METHODS

Data were obtained from repeated experiments on 10 normal subjects (5 male; 5 female; aged 19 to 47 years), all of whom had given informed consent to the experimental procedures. The subjects reclined awake on a comfortable couch with the left foot secured to a footplate attached to the drive-shaft of a servo-controlled printed circuit motor (*cf.* Burke, McKeon, Skuse and Westerman, 1980). The lower limb was supported by pillows with the knee and hip joints slightly flexed so that the lower leg was in the horizontal plane. This arrangement minimized transmission to the body of the mechanical disturbance resulting from abrupt passive movements of the ankle. The initial angle of the ankle joint was set routinely at 24 degrees plantar flexion.

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The motor was driven with feedback of position and velocity so that a step change in voltage of appropriate amplitude produced an abrupt plantar flexion movement of the foot through an amplitude of 3.5 degrees at a peak velocity of 67 to 100 deg s^{-1}. The duration of the step, and therefore of the plantar flexion movement, was varied randomly between 100 ms and 350 ms so that the potentials evoked by the return dorsiflexion were not synchronized to the plantar flexion movement. A standard stimulus repetition rate of 1 Hz was used, except when specifically studying the effects on the evoked potential of varying the repetition rate. Throughout each recording session, subjects remained awake, listening to white noise through earphones, to mask the noise of the motor.

Cerebral evoked potentials were recorded from the scalp using silver cup electrodes secured with collodion. The electrode impedance was at or below 5 kΩ. Except when constructing detailed maps of the scalp distribution of the evoked potential the recordings were made between Cz (in the 10–20 system of electrode placement) and an indifferent reference. In a number of control sequences, Fpz, A1 and the Inion were found to be equally satisfactory as reference sites, since the components of the evoked potential could not be discriminated when recording between any two of these three sites. However, less muscle artifact was recorded using Fpz, and this site was therefore used as the standard reference point. The activity from the scalp electrodes was amplified (gain 50,000), filtered (1.6 Hz to 3.2 kHz) and stored on tape (linear frequency response DC-2.5 kHz), together with the waveform driving the motor, the output of a potentiometer recording ankle joint position, and the surface electromyogram (EMG) of the pretibial flexor muscles.

The major purpose of the study was to characterize the cerebral potential evoked by passive plantar flexion of the ankle—its reproducibility in the same subject throughout a recording session and between different recording sessions; its variability between subjects; and its scalp distribution. This potential was also compared with that evoked by passive dorsiflexion of the ankle and that evoked by electrical stimulation of the sural nerve at the lateral malleolus. For the latter potential, the stimuli were 0.2 ms duration pulses, at a voltage sufficient to produce a maximal sensory action potential in surface electrodes situated over the nerve, 16 cm proximally. To determine the parameters of the plantar flexion stimulus critical for evoking the potential, the stimulus repetition rate and the amplitude, velocity and acceleration of movement were varied systematically. To help characterize the likely receptor population(s) responsible for the evoked potential, a series of nerve block experiments were performed using: (i) a sphygmomanometer cuff inflated above the ankle joint to 300 mmHg until anæsthesia had developed distal to the cuff; (ii) pressure applied to the peroneal nerve at the fibular head using a U-clamp until severe weakness had developed in the distribution of the nerve; and (iii) infiltration of lignocaine 1 per cent around the peroneal nerve at the fibular head, sufficient to produce severe weakness of the pretibial muscles.

In five subjects, multi-unit recordings of muscle afferent activity were recorded directly from fascicles of the peroneal nerve innervating the pretibial flexor muscles using tungsten microelectrodes inserted manually through the skin into the appropriate nerve fascicle. The experimental technique has been described in full previously (Hagbarth and Vallbo, 1968; Burke, Hagbarth, Lŏfstedt and Wallin, 1976). No attempt was made to obtain single unit recordings since the discharge pattern of a single afferent might not be representative of the population response. The parameters of the plantar flexion stimulus were varied as in the cerebral evoked potential studies to determine the relationship between the responsiveness of muscle mechanoreceptors and the latency and amplitude of the cerebral evoked potential.

In five subjects the cerebral potential evoked by percussion of the tendon of the tibialis anterior muscle was recorded. Tendon percussion was performed by a small vibrator (Ling-Altec, type 201), driven by square-wave pulses of duration 240 ms at repetition rates of 1 Hz and 0.2 Hz. In one experiment, needle electrodes were inserted into the skin immediately distal to the percussion site to determine whether cutaneous stimulation at a level sufficient to produce a pricking pain sensation was adequate to evoke a detectable cerebral potential. The percussion-evoked and cutaneous-evoked potentials were also recorded after anæsthetizing the skin with lignocaine 1 per cent in a radius of 2.5 cm around the site of tendon percussion and cutaneous stimulation.

All data were monitored continuously during the experiment, and the evoked potential (Cz–Fpz) was averaged on-line during each recording sequence using a fixed-programme averaging computer (DAV6 Averager and AX6 Averager Expander, Medelec Ltd) with an analysis time of 200 ms and 1024 ordinates. Definitive data analysis was performed off-line using a programmable computer (LAB8/E, Digital Equipment Corporation) usually with four data channels, an analysis time of 250 ms and 500 ordinates/channel.

RESULTS

Passive plantar-flexion movements of the ankle joint at 1 Hz evoked a cerebral potential (fig. 1), which had a mean latency of onset of 37.1 ms. The potential consisted of a small biphasic positive wave (with mean peak latencies of 46.6 and 64.7 ms), a prominent negative wave (88.6 ms) and a subsequent more variable

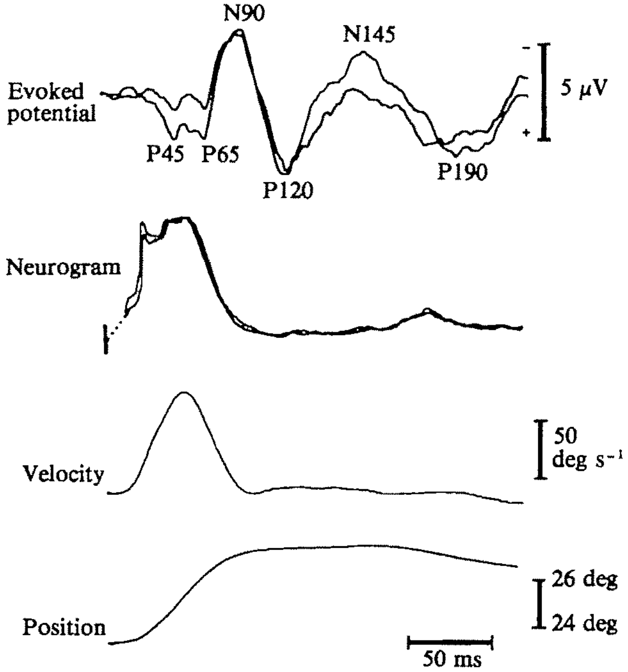

FIG. 1. To show two superimposed averages of cerebral evoked potentials (Cz referenced to Fpz), *top trace*, and of muscle afferent activity (integrator time constant (0.01 s), recorded by a microelectrode within a fascicle of the peroneal nerve innervating tibialis anterior (*second trace*); the velocity profile of the plantar-flexion movement of the ankle (*third trace*); and ankle joint position (*bottom trace*). The repetition rate of stretch was 1 Hz. The components of the evoked potential are labelled according to polarity at the vertex electrode (P, positive; N, negative) and approximate latency in ms in normal adults. Peak velocity of movement is reached at 46 ms, maximum muscle afferent activity at 37 ms, and the onset of the initial deflection of the evoked potential at 32 ms.

TABLE 1. LATENCY OF CEREBRAL POTENTIALS EVOKED BY PASSIVE PLANTAR FLEXION OF THE ANKLE

	Mean	*SD*
P45	46.6 ms	3.0
P65	64.7 ms	4.9
N90	88.6 ms	9.1
P120	118.7 ms	12.6
N145	146.0 ms	12.8
P45/65–N90	5.3 μV	2.5

P = positive. N = negative.

positive-negative-positive complex (118.7, 146 and 190 ms)—*see* Table 1. The initial deflections of the cerebral evoked potential were of short latency when compared with both the profile of the movement and the muscle afferent response to the same movement (fig. 1). Indeed, although the initial deflection in the cerebral evoked potential occurred approximately 35 ms after the onset of the muscle afferent response, it usually started at about the same time as both the velocity of movement and the muscle afferent activity had reached their peaks.

The general form of the cerebral potentials evoked by plantar flexion movements were similar amongst the different subjects, but the amplitudes of the different components were more variable (fig. 2, left column). There was no obvious

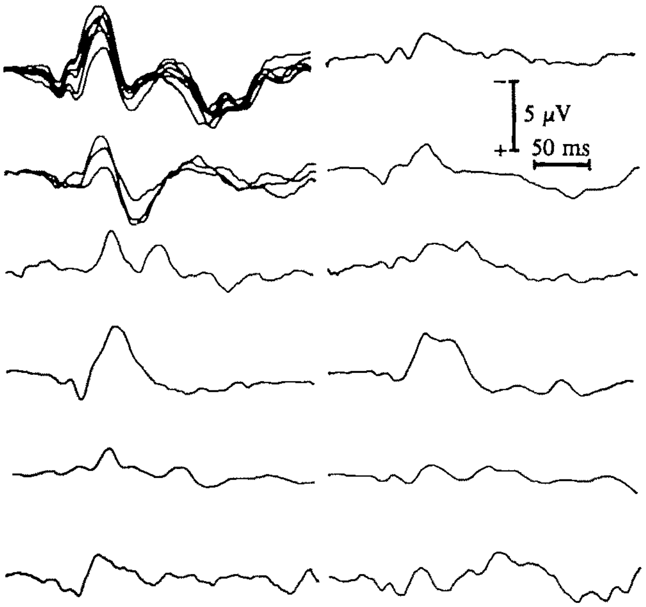

FIG. 2. To show cerebral potentials evoked by plantar flexion movements (*left column*) and dorsiflexion movements (*right column*) of the ankle for 6 subjects. The superimposed traces to plantar flexion for the first subject are from 6 separate sequences, each of 500 stretching movements, recorded over a two-hour period to show the reproducibility of the response. The superimposed averages for the second subject were obtained during 3 different recording sessions.

correlation between the latency of the inital positive wave and such variables as age, height or gender, although the sample size was too small to extract the contributions of these variables. The cerebral potentials were quite consistent in any one subject when repeated on the same day (fig. 2, top traces in left column) and were reasonably so on separate days (fig. 2, second set of traces in left column). The cerebral potentials evoked by passive dorsiflexion of the ankle joint were essentially similar, although the early biphasic positive wave was sometimes not as well formed (fig. 2, right column). This difference probably arose from slight differences in the velocity and acceleration of the plantar flexion and dorsiflexion movements. Due to the inertia of the foot it was difficult to achieve the same velocity with dorsiflexion as with plantar flexion.

Scalp Distribution

In three subjects the scalp distribution of the potential evoked by passive plantar flexion of the ankle joint was compared with that of the potential evoked by stimulation of the sural nerve at the lateral malleolus (fig. 3). The initial component

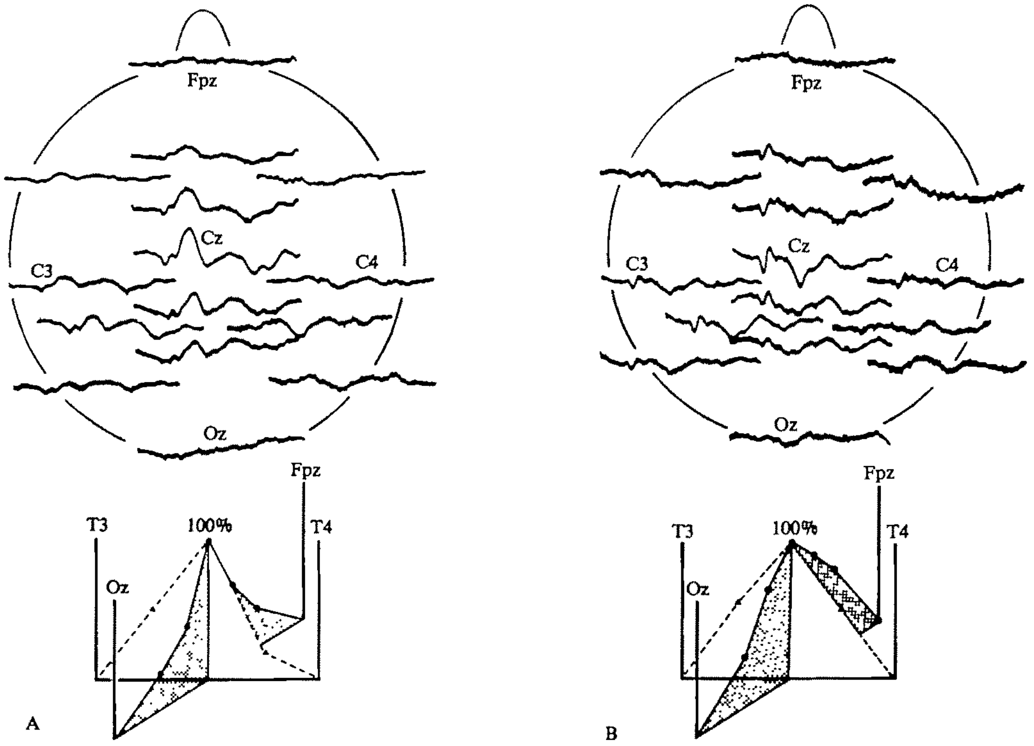

FIG. 3. To show the scalp distribution of potentials evoked by plantar flexion of the ankle (A) and by electrical stimulation of the sural nerve at the ankle (B) in one subject. The amplitudes of the initial positive-negative complexes (P45–65 to N90 for plantar flexion; P45 to N50 for sural nerve stimulation) are plotted below, expressed as a percentage of the amplitude of that complex at Cz: Note that the amplitude of the potential is maximum at Cz and diminishes rapidly in either plane for both methods of stimulation. There were no detectable potentials at T3, T4 and cervical region; these recordings have therefore been omitted from the maps.

of the latter potential was a monophasic positive wave of slightly longer latency than the initial component of the former potential. With both potentials, the amplitudes of the early and late components were maximal at Cz. The amplitudes of both the early and the late components were significantly smaller when the recording site was displaced by 3.5 cm in the sagittal or coronal planes. The scalp distribution of the potential evoked by passive dorsiflexion was similar in the only subject in whom this was specifically examined. These findings suggest that the early and the late components of the potentials arise from a fairly restricted generator, close to the midline at Cz.

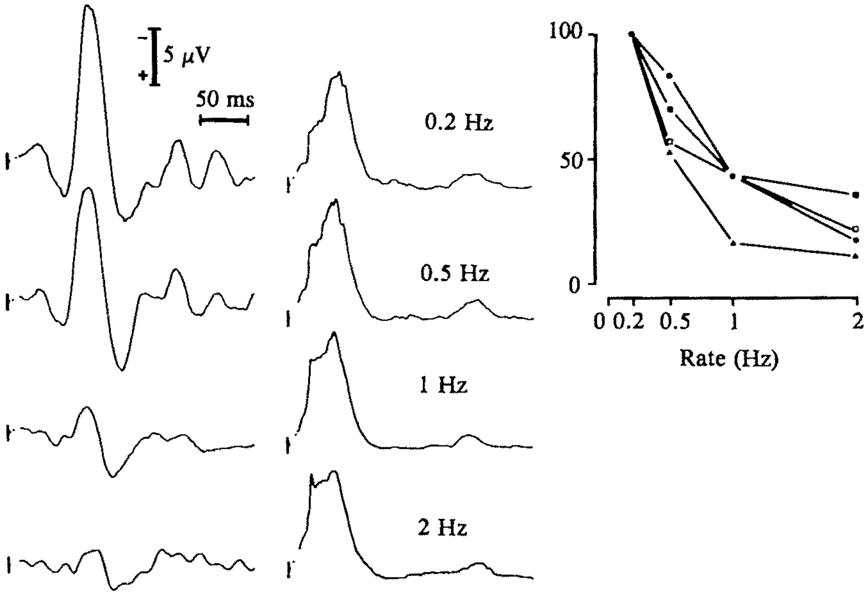

FIG. 4. To show the effects of the repetition rate of plantar flexion movements on both the averaged cerebral potential (*left column*) and the muscle afferent activity of tibialis anterior (*right column*) in the same subject. The graph shows the amplitudes of the initial positive-negative complex of the evoked potential (P45-65 to N90) as a function of the repetition rate for this and three other subjects. The amplitude at the slowest rate, 0.2 Hz, was set to be 100 per cent and the amplitudes at the other rates adjusted accordingly. Stimulus repetition rate has profound effects on the amplitude of the evoked potential but is without effect on the amplitude of the muscle afferent activity. For the muscle afferent activity the integrator time constant was 0.01 s.

The Effects of Varying Stimulus Parameters

Repetition rate had profound effects on the amplitudes of the potentials evoked by passive plantar flexion, but not on their latencies (fig. 4). The potentials were largest with the slowest rate (0.2 Hz), and were attenuated by more than 50 per cent when the stimulus rate was increased to 1 Hz. In contrast, the amplitude of the muscle afferent response from the pretibial flexor muscles to the same perturbations did not differ significantly at these stimulus rates.

Since a repeated plantar flexion stimulus requires restitution of the ankle to the initial starting position before the stimulus can be delivered again, there are two possible causes for the attenuation of the evoked potentials at high stimulus repetition rates: (i) the higher repetition rate of the plantar flexion stimulus; and (ii) an interaction due to the proximity of the preceding dorsiflexion. A similar but less pronounced dependence on repetition rate was seen with the potentials evoked by percussion of the tendon of tibialis anterior. This stimulus evoked a cerebral potential very similar to that evoked by passive plantar flexion (*see later*, fig. 8). Hence it is likely that the cerebral potential would be attenuated if plantar flexion stimuli could be delivered in isolation at high rates. The second possibility was investigated by delivering a conditioning dorsiflexion at a fixed interval of 500 ms before the test plantar flexion, and by then varying the repetition rate of this stimulus complex (*cf.* fig. 5A). The interval of 500 ms was chosen since the dorsiflexion movement evoked no detectable late components at this latency. When the repetition rate of this complex was decreased from approximately 0.5 Hz to 0.25 Hz, one would expect the potentials evoked by plantar flexion to be augmented to a similar extent as those evoked by dorsiflexion, if the pathways involved in their generation were completely independent. This was not the case (fig. 5B). Decreasing

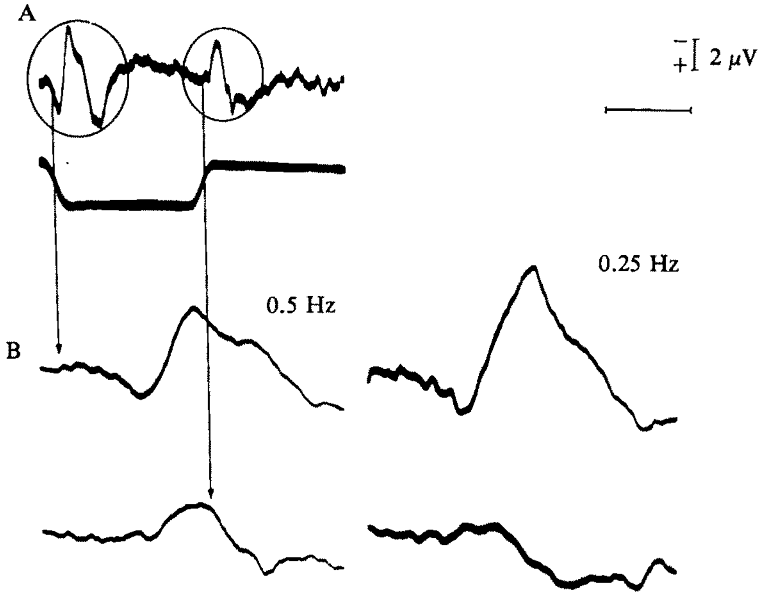

FIG. 5. To show the effects of the proximity of an immediately preceding dorsiflexion movement of the ankle on the potentials evoked by plantar flexion at two stimulus repetition rates. The paradigm is depicted in A on a slow time-base, and shows the potentials (*upper trace*) evoked by an initial dorsiflexion movement of the ankle followed 500 ms later by those evoked by a return plantar flexion. The evoked potentials to these two movements are shown in B on a faster time-base as a function of the stimulus repetition rate. The upper set of potentials are due to the dorsiflexion movements; the lower set to the plantar flexion movements. Note that a slowing of the repetition rate is accompanied by the expected increase in the amplitude of the evoked potential to dorsiflexion whereas the potential due to the immediately following plantar flexion movement becomes smaller. Horizontal calibration: 250 ms for A; 50 ms for B.

the repetition rate from approximately 0.5 Hz to approximately 0.25 Hz did result in augmentation of the potential evoked by dorsiflexion, there being an increase in amplitude of the largest component (P45/65–N90) by 62 per cent. However, this change in rate also resulted in *attenuation* of the potential evoked by plantar flexion by 65 per cent. It can therefore be concluded that there is an inhibitory interaction between the pathways activated by dorsiflexion and plantar flexion movements, and that this factor as well as the higher repetition rate of the same stimulus contributes to the attenuation of the evoked potentials seen in fig. 4.

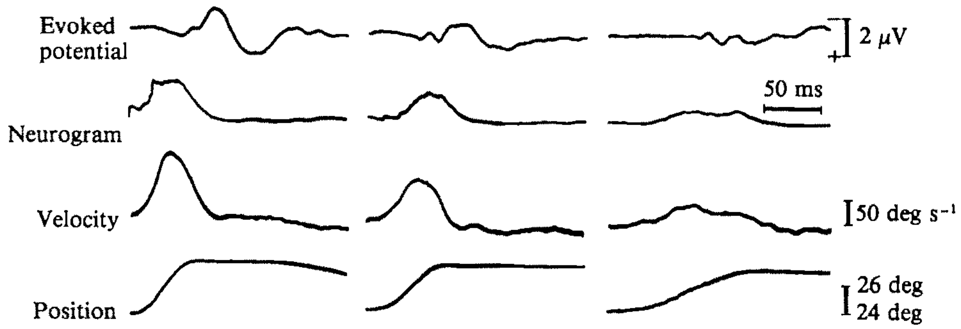

FIG. 6. To show the effects of slowing the plantar flexion movement on the cerebral evoked potential (*top trace*) and the muscle afferent activity of tibialis anterior (*second trace*). The velocity of the movement is shown in the *third trace* and joint position in the *fourth trace*. Note that both the latency of the evoked potential and the peak of the integrated neural activity are delayed and that their amplitudes are attenuated with movements of slower velocity.

When the peak velocity of the movement was varied, the amplitudes and latencies of the components of the cerebral potential were altered (fig. 6). The muscle afferent response to the movement changed in parallel with the velocity of the movement (fig. 6). However, since the earliest component of the cerebral evoked potential occurred at about the same time as the movement reached peak velocity, this measure is unlikely to be the major factor determining the latency and amplitude of the evoked potential. To differentiate between the effects resulting from changing the velocity of movement and those due to changing its acceleration, the servo motor was driven by waveform which had an initial transient of high amplitude designed to drive the motor maximally for a brief period of time. In this way it was forced to produce maximum acceleration despite changes in the amplitude of movement and its peak velocity. The evoked potentials were remarkably consistent (fig. 7), even though there was a decrease in the amplitude and the peak velocity of movement by 50 per cent and 35 per cent respectively. Thus, superficially, acceleration of movement appears to be a more important factor than amplitude and peak velocity in evoking the cerebral potential.

Potentials Evoked by Tendon Percussion

Percussion directly on the tendon of tibialis anterior evoked cerebral potentials which differed from those evoked by passive plantar flexion only in latency and, to

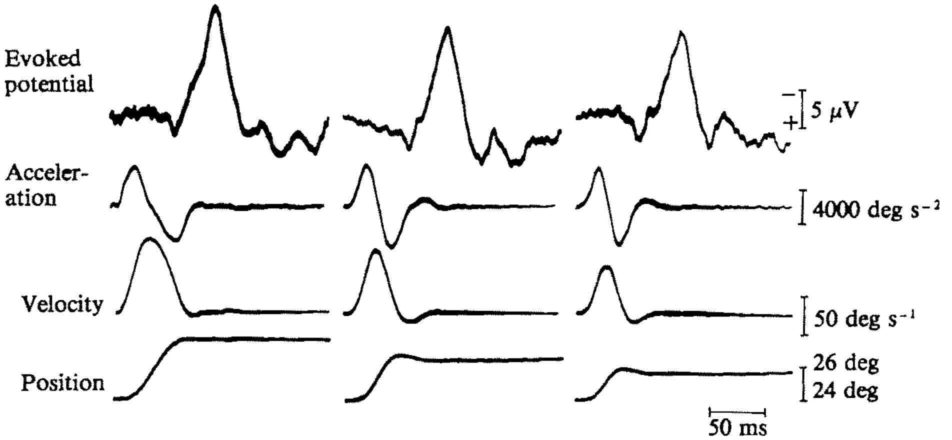

FIG. 7. To show the effects on the cerebral evoked potential of maintaining the acceleration of the plantar flexion movement constant while altering both the amplitude and the peak velocity of the movement. The profiles for acceleration are contained in the *second trace*, velocity in the *third trace*, and joint position in the *lowest trace*. The amplitudes of the components remain relatively constant even though both the extent of plantar flexion and the peak velocity are markedly reduced.

a lesser extent, amplitude (fig. 8). The early components occurred approximately 6 to 8 ms earlier with tendon percussion than with passive ankle movements, a difference attributable to the low inertia of the vibrator. In different subjects the onset of the first positive wave evoked by tendon percussion occurred at 28 to 36 ms and its peak occurred at 36 to 41 ms. Although the tendon percussion was restricted

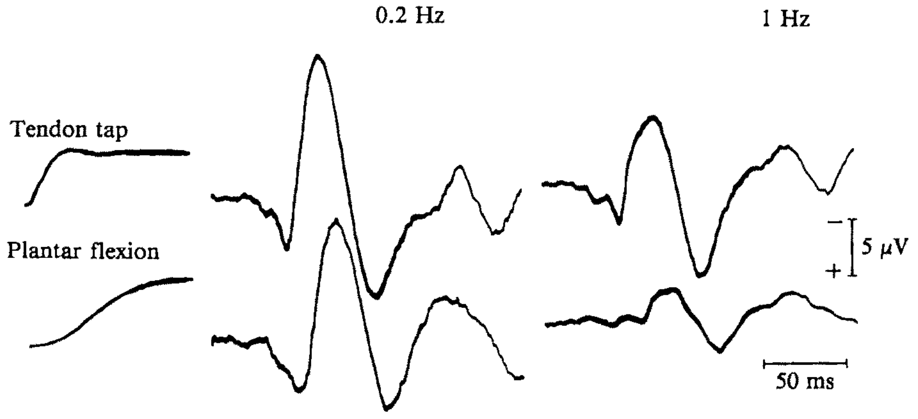

FIG. 8. To show the similarity of the cerebral potentials evoked by percussion on the tendon of tibialis anterior (*upper traces*) and passive plantar flexion of the ankle (*lower traces*) at two stimulus repetition rates (0.2 and 1 Hz). The profiles of the two stimuli are recorded on the left of the figure: force of percussion on the tendon, ankle position, respectively. The potentials are similar, but the components evoked by percussion occur 8 to 9 ms before those evoked by plantar flexion. Stimulus repetition rate affected the amplitude of the potential evoked by plantar flexion movements to a greater extent than that evoked by tendon percussion.

to tibialis anterior and the skin at the site of percussion, the amplitudes of the components of the evoked potential were often higher and the effects of repetition rate were less prominent than with plantar flexion movements (fig. 8). This could have been so both because the inhibitory effects of dorsiflexion would have reduced the size of the potential evoked by plantar flexion, and because the servo motor was not capable of producing as abrupt a stimulus as the vibrator. If the site of percussion was displaced slightly so that it was not directly over the tendon, the components of the cerebral evoked potential were of lower amplitude and of longer latency.

In one subject electrical stimulation of the skin 1 cm distal to the site of percussion evoked a low amplitude potential, the earliest component of which was a positive peak at 57 ms and the largest component of which measured 5 μV. In this subject, the first positive peak of the percussion-evoked potential occurred at 41 ms and the largest component measured 18 μV. Anæsthesia of the skin within a 2.5 cm radius of the point of percussion abolished the potential evoked by cutaneous stimulation but did not affect the potential evoked by tendon percussion.

It is concluded that muscle stretch produced by percussion of the tendon of tibialis anterior is adequate to produce a cerebral evoked potential virtually identical to that evoked by passive plantar flexion of the ankle joint.

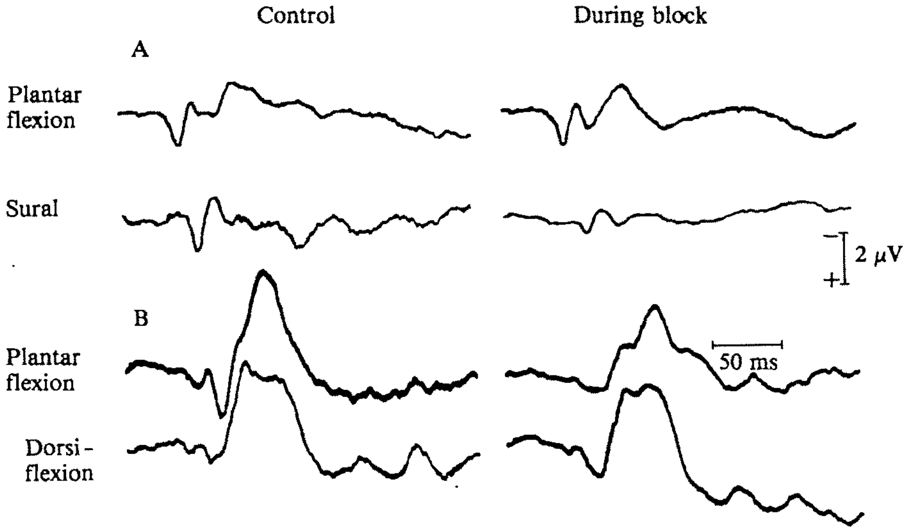

FIG. 9. To show the effects of various nerve blocks on the cerebral potentials. In A, an ischæmic/pressure block just above the ankle resulted in attenuation of and delay in the potential evoked by stimulation of the sural nerve (*lower traces*), but the potential evoked by plantar flexion movements was unchanged (*upper traces*). In B, a local anæsthetic block of the peroneal nerve at the fibular head resulted in attenuation of and delay in the components of the potential evoked by plantar flexion (*upper traces*) but the potential evoked by dorsiflexion was unaffected (*lower traces*).

Nerve Blocks

To confirm that muscle stretch was the stimulus responsible for generating the cerebral evoked potential, a series of nerve block experiments was performed. In two subjects, an ischæmic pressure block was induced by inflation of a sphygmomanometer cuff around the leg above the ankle. At the stage of complete cutaneous anæsthesia distal to the cuff, the cerebral potential evoked by electrical stimulation of the sural nerve was abolished in one subject and attenuated and delayed in the second (fig. 9A). In both subjects there was no change in the potentials evoked by passive plantar flexion. It is concluded that the plantar flexion-evoked potential results from receptors proximal to the ankle joint.

The peroneal nerve was blocked at the level of the fibular head by local anæsthetic in one subject and by pressure in a second subject. With the pressure block, the components of the cerebral potential evoked by plantar flexion were attenuated by 30 to 50 per cent, but there were no changes in latency. With the local anæsthetic block, the potential components were both attenuated and delayed (fig. 9B). In neither case was there any significant alteration of the cerebral potential evoked by passive dorsiflexion movements.

It is concluded that the major contributors to the cerebral potential evoked by passive plantar flexion of the ankle joint are mechanoreceptors located in the distribution of the peroneal nerve proximal to the ankle joint.

Electrical Stimulation of Muscle Afferents

In five subjects electrical stimuli were delivered through a microelectrode inserted into a fascicle of the peroneal nerve innervating one of the pretibial flexor muscles. Recordings made through the same microelectrode demonstrated that the intrafascicular site was dominated by afferents innervating muscle mechanoreceptors which responded at low threshold to muscle stretch and to tendon percussion. There was no detectable neural discharge in response to cutaneous stimuli. Electrical stimuli delivered through the microelectrode failed to evoke any cutaneous sensation.

Stimulation within muscle nerve fascicles was insufficient to produce a detectable cerebral potential if the stimulus intensity was below that required to produce a direct EMG response. In one subject, a consistent cerebral potential (amplitude of the largest component 10 μV) could be evoked by stimuli which produced a muscle twitch involving only two motor units (as judged by all-or-none behaviour of the compound EMG action potential). In the other four subjects the necessary stimulus evoked an EMG response which measured 12 to 20 per cent of the maximal compound EMG action potential of the same muscle. The electrically-evoked cerebral potential was of the same general form as the potential evoked by passive plantar flexion of the ankle but occurred up to 14 ms earlier (fig. 10). The components of the cerebral potential evoked by electrical stimulation of muscle

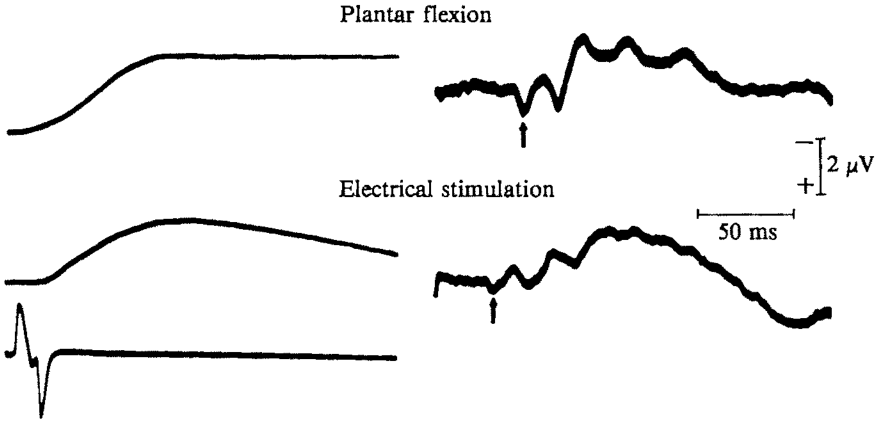

FIG. 10. To show the similarity between the cerebral potentials evoked by plantar flexion (*upper trace*) and by electrical stimulation of muscle afferents from tibialis anterior (*lower traces*). The vertical arrows indicate the initial positive components of the evoked potentials. The electrically-evoked components precede those evoked by passive plantar flexion by 14 ms. The traces on the left are: ankle position (*upper trace*); torque and EMG produced by the twitch contraction of tibialis anterior.

afferents occurred at too short a latency to be attributable to changes in afferent activity associated with the twitch contraction (fig. 10).

In two subjects the microelectrode was inserted into three cutaneous fascicles of the peroneal nerve. One supplied the lateral aspect of the dorsum of the foot, extending medially to toe 3, the second innervated the skin of toes 1 and 2 and the adjacent dorsum, and the third the skin overlying the lateral compartment of the leg. Stimulation in each fascicle at a level producing a non-painful pricking sensation in the distribution of the fascicle evoked a cerebral potential of different morphology to that evoked by stimulation of muscle afferents, identifiable early components occurring 9 to 14 ms later with cutaneous afferent stimulation.

It may be concluded that direct activation of muscle afferents can evoke a cerebral potential similar to that evoked by passive plantar flexion movements, but that direct activation of cutaneous afferents does not do so.

DISCUSSION

This study has shown that passive plantar flexion movements of the ankle are capable of evoking a reproducible cerebral potential in normal subjects. The stimulus is, however, not selective for any particular receptor, and it would be naïve to suggest that a particular receptor type was solely responsible for the cerebral potential. Nevertheless, it is possible to draw some tentative conclusions about the mechanoreceptors responsible for the cerebral evoked potential.

Joint movement *per se* is not necessary to produce the potentials: first, prolonged anæsthesia of the foot using a cuff above the ankle joint did not alter the potential significantly, and, secondly, percussion on the tendon of tibialis anterior at a site distal to the ankle joint evoked an identical potential. Under the prevailing conditions, stretch of cutaneous or muscular mechanoreceptors was probably the major factor responsible for the evoked potential. The skin of the foot did not play an indispensable role since both the movement-evoked potential and the percussion-evoked potential were not altered by an ischæmic/pressure block and a local anæsthetic block, respectively. The skin overlying the pretibial flexor muscles would have been subjected to some stretch with passive ankle movements but not with tendon percussion. The only receptors to be activated under all experimental conditions were mechanoreceptors in the pretibial flexor muscles. Furthermore, a similar cerebral potential could be evoked by electrical stimulation within muscle nerve fascicles, when the only afferents to be activated were of muscle origin.

Pacinian corpuscles are found occasionally and Paciniform corpuscles more commonly in muscle, muscle fascia and periarticular connective tissue (Matthews, 1972). These receptors are sparse in total number, particularly when compared with muscle spindles and Golgi tendon organs, and they cannot be considered 'stretch receptors'. Any corpuscles in the pretibial muscles would have been activated by the abrupt muscle stretch, but, overall, their contribution to the cerebral evoked potential is likely to be small. Golgi tendon organs are known to be relatively insensitive to passive stretch in the absence of background muscle contraction (Houk and Henneman, 1967; Stuart, Mosher, Gerlach and Reinking, 1972). The passive stretch used in the present study would therefore have been a relatively ineffective stimulus to the population of tendon organs in the pretibial muscles, although it is highly probable that individual tendon organs would have been activated. It is well-established that muscle spindle endings are extemely sensitive stretch receptors: both the passive plantar flexion movement and the tendon percussion would have been potent stimuli to these endings. Afferents from primary and secondary spindle endings project to cortex (*cf.* for example, Phillips, Powell and Wiesendanger, 1971; Lucier, Rüegg and Wiesendanger, 1975; Hore, Preston, Durkovic and Cheney, 1976), and appeared to be involved in the awareness of limb position and movement (*cf.* McCloskey, 1978). Although a contribution from other receptors cannot be excluded, spindle endings in the pretibial flexor muscles could well be the major source of the afferent activity responsible for the cerebral potential evoked by passive plantar flexion movements.

Relationship between Receptor Response and the Properties of the Cerebral Evoked Potential

If it can be assumed that muscle spindle afferents are responsible for the cerebral evoked potential, some of the properties of the potential can be explained only by the additional assumption that the incoming afferent activity is subjected to modification by the central nervous system. Specifically, the dependence of the evoked potential on the repetition rate of the stimulus cannot be explained on a receptor basis, though this property has well-established precedents in the evoked potential literature (for example, Davis, Mast, Yoshie and Zerlin, 1966; Regan, 1972). In addition, the inhibitory interaction between the pathways activated by passive dorsiflexion and by passive plantar flexion does not occur at receptor level. However, if the underlying process is analogous to reciprocal innervation, it too has adequate precedent in the motor control literature (for example, Creed, Denny-Brown, Eccles, Liddell and Sherrington, 1932).

The response of primary muscle spindle endings to large amplitude stretch can be adequately characterized by an equation which incorporates velocity and length terms (Matthews, 1972). The cerebral evoked potentials, however, would be better characterized by an additional derivative of muscle length, possibly acceleration. If this does represent a true dependence on acceleration, the nervous system can be said to operate as a high-pass filter, adding an additional differentiation to the incoming afferent volley. In the relaxed state, the nervous system appears to respond only to the 'leading edge' of the incoming afferent volley. Whether the transmission through central afferent pathways is similar when a subject actively opposes a perturbation remains to be established, but there is no reason to suppose that it should be so (*cf.* Neilson and Lance, 1978).

Central Pathways

No information is available from this study on the transmission to cerebral level of the afferent volley responsible for the evoked potential, and no firm conclusions can be drawn about the generators of the different components of the potential. In the scalp recordings, both the early and late components of the potential were discretely localized to Cz, suggesting that the generators were situated under or very close to that recording electrode. It cannot be maintained that the components are of cortical origin but, at the very least, they probably reflect activity of large fibre tracts relaying information to and from cortex. The latency for the onset of the first deflection of the evoked potential, the 'P45' component, was as little as 30 ms with tendon percussion and even shorter (27 ms) with electrical stimulation of muscle afferents. If up to 5 ms is allowed for the inertia of the vibrator and for receptor transduction and at least 15 ms for afferent conduction to the spinal cord, one can conservatively estimate central conduction time to a near-cortical level at approximately 10 and certainly less than 15 ms. This suggests a fast oligosynaptic pathway.

Clinical Significance

Somatosensory potentials evoked by electrical stimulation of a peripheral nerve trunk and recorded using scalp electrodes are now accepted diagnostic procedures (Halliday, 1978; Starr, 1978). Potentials evoked by physiological activation of cutaneous mechanoreceptors have also been described (*cf.*, for example, Pratt, Amlie and Starr, 1979). The present study provides evidence that physiological activation of muscle mechanoreceptors may evoke a reproducible cerebral potential.

If the potentials evoked by activation of receptors differed from those evoked by electrical stimulation of afferent fibres only in that the former were elicited in a 'more physiological' way, there would be little purpose in setting up a technically more demanding procedure. However, a physiological stimulus tests the transmission in neural pathways under conditions which more closely resemble the natural state, and, theoretically at least, is more likely to demonstrate functionally important deficits. More importantly, the physiological stimulus does not bypass the receptor, a factor of particular significance with muscle spindle endings since their responsiveness can be altered by fusimotor activity.

The present data on the cerebral projection of muscle afferents are relevant not only to experiments on kinæsthesia (*cf.* McCloskey, 1978) but also to the long-latency (possibly long-loop, possibly transcortical) reflexes which may be demonstrated in man in response to abrupt muscle stretch or its equivalent (Marsden *et al.*, 1973; *cf.* Desmedt, 1978). If the latencies reported in the present study are compared with those of the long-latency reflex response of flexor hallucis longus (74 ms in C. D. Marsden; 90 ms in P. A. Merton, *cf.* Marsden, Merton and Morton, 1976), there is adequate time for the long-latency reflex to be transmitted over a transcortical reflex pathway, as was postulated by these authors. Abnormalities of 'transcortical' reflexes have been implicated in some forms of reflex myoclonus (*cf.* for example, Dawson, 1947; Halliday, 1967; Chadwick, Hallett, Harris, Jenner, Reynolds and Marsden, 1977; Shibasaki, Yamashita and Kuroiwa, 1978) and in parkinsonian rigidity (Tatton and Lee, 1975). A study of the cerebral potential evoked by muscle stretch may shed further light on any such abnormality.

SUMMARY

The cerebral potentials evoked by passive plantar flexion movements of the ankle were recorded by scalp electrodes in normal human subjects. The potential consisted of a biphasic positive wave (P45, P65), a prominent negative wave (N90), and a subsequent positive-negative-positive complex (P120, N145, P190). The components of the potential were of largest amplitude at the vertex, small displacements of the active recording electrode resulting in a marked decrease in amplitudes. The amplitudes of the components were also profoundly affected by changes in the repetition rate of the stimulus and by changes in the acceleration of the stretching movements; they were little affected by changes in the extent or peak velocity of stretch provided that acceleration remained constant. Potentials of similar morphology but of slightly shorter latency could be evoked by percussion of the tendon of tibialis anterior and by electrical stimuli delivered through a microelectrode inserted into a pure muscle nerve fascicle of the peroneal nerve innervating one of the pretibial flexor muscles. The results of nerve block experiments (ischæmic/pressure block above the ankle; pressure block and local anæsthetic block of the peroneal nerve at the fibular head) suggest that the afferents responsible for evoking the cerebral potential arose from muscle mechanoreceptors.

It is concluded that information about muscle stretch arising from muscle mechanoreceptors (probably muscle spindle endings) reaches the cerebral hemispheres of man at short latency and that the resulting potentials can be readily detected using scalp electrodes.

ACKNOWLEDGEMENTS

A.S. was a recipient of a Senior International Fellowship from the Fogarty Foundation, National Institutes of Health, Bethesda, Maryland. The project was supported by the National Health and Medical Research Council of Australia and the NIH. The authors are grateful to Drs J. W. Lance and A. K. Lethlean for further support and encouragement.

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(*Received May 29, 1980*)

Brain (1981), **104**, 167–186

REACTION TIME IN PARKINSON'S DISEASE

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INTRODUCTION

WILSON (1925) was the first to obtain quantitative measures showing impairments of reaction time (RT) in Parkinson's disease, reporting values '. . . of 0.24 seconds for normal individuals and 0.36 seconds for subjects with paralysis agitans.' Some subsequent studies have confirmed Wilson's findings, while others have failed to observe RT deficits in parkinsonians. However, even when RT deficits have been observed, the deficits have usually been relatively minor. In spite of these past inconsistencies, we thought that RT measurements might still be useful in studies of the nature of the motor disorder in parkinsonism if the RT measurements were combined with measurements of movement speed and recordings of the electromyographic correlates of RT movements performed by parkinsonians. The present report describes the results of our observations on these matters.

SUBJECTS AND METHODS

The results to be reported were obtained in normal subjects and in parkinsonians under treatment in studies aimed at ascertaining the comparative effectiveness of bromocryptine and L-Dopa. In both groups of subjects practice trials were administered until it was clear that subjects had a full understanding of the task requirements. The RT responses made by the subjects involved pronation-supination arm movements (fig. 1) during which biceps EMG was recorded, the biceps being active with supination and inactive with pronation. The handle grasped by the subject was coupled to the axle of a brushless D.C. torque motor (Aeroflex TQ-52) which delivered kinæsthetic stimuli in tests of kinæsthetic RT (Colburn and Evarts, 1978). EMG activity and handle position were recorded on magnetic tape together with signals providing information as to times of occurrence of visual and kinæsthetic stimuli. Data were quantitatively analysed by a PDP-12 computer program (Evarts and Vaughn, 1978) available from the DECUS Program Library of the Digital Equipment Corporation, Maynard, Massachusetts.

For both visual RT and kinæsthetic RT, the lamps illustrated in fig. 1 provided DIRECTION signals specifying the direction of the movement (pronation or supination) to be made, and a lamp at the centre provided a READY signal. In tests of kinæsthetic RT, the GO stimulus was a handle displacement produced by the torque motor, while for tests of visual RT the GO stimulus was illumination of a lamp marked GO. The READY lamp and the right or left DIRECTION lamp came on at the same time and the GO signal came on 2 to 4 s later. This allowed the subject 2 to 4 s to get set to pronate or supinate prior to the GO signal. Directions of successive movements and intervals between READY and GO stimuli varied unpredictably from one trial to the next. Occurrences of READY and GO stimuli were contingent on the handle being in a 5 deg zone (2.5 deg on either side of the vertical). Visual RT was scored as the interval between GO and the handles being moved out of this 5 deg zone. The movements performed by the subjects involved rotating the handle until an external stop terminated handle movement after a 45 deg displacement. Movement time (MT) was scored as the interval between the initial 2.5 deg movement and completion of the 45 deg pronation or supination. For the kinæsthetic RT paradigm, the initial handle displacement could not be used as an indicator of RT since the GO signal itself was a handle displacement. Procedures used in kinæsthetic RT scoring will be described in connection with the kinæsthetic RT results.

Observations on both kinæsthetic and visual RT were obtained in 29 parkinsonians (median age 61 years, range 38 to 72 years), 21 elder control subjects (median age 70 years, range 52 to 80 years), and 11 younger control subjects (median age 23 years, range 20 to 45 years).

RESULTS

Our presentation of results relies heavily on Tables, and we believe that a word of justification is required because it might seem that we are confronting the reader with excessive quantities of raw data. In our defence we would like to point out that

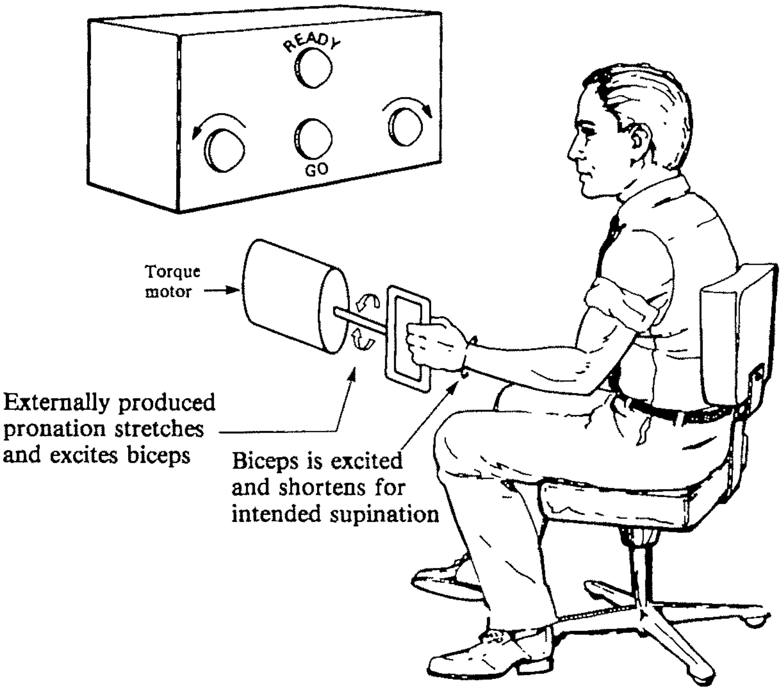

READY
GO
Torque motor
Externally produced pronation stretches and excites biceps
Biceps is excited and shortens for intended supination

FIG. 1. Paradigm for RT testing. In tests of simple visual RT, subjects maintained the handle vertical for 2 to 4 s and then the READY lamp together with one of the two direction lamps (↙ or ↘) came on simultaneously. Following an additional delay, the visual GO signal came on to trigger the RT movement. For choice visual RT, the READY lamp came on alone, and then GO and direction lamps came on simultaneously, thus depriving the subject of the opportunity to pre-program the direction of movement. For kinæsthetic RT, the visual GO lamp was masked, and the GO stimulus was a handle displacement produced by the torque motor.

each score of an individual subject given in the Tables is in fact the median for a number of trials by the subject, so that we are not actually presenting raw scores at all. But it could still be argued that a single summary Table (such as our Table 4) would suffice, and that Tables 1, 2 and 3 are not needed. We believe that the justification for describing the performance of the individual subjects lies in the high degree of variability between different subjects and between directions of movement and right and left sides for a given subject. It seemed to us that it was important to call attention to this variability, and the presentation of data on the performance of individual subjects seemed to us to be the most effective way to do this. We would thus urge the reader to scan the Tables attentively, for in them will be seen evidence of

TABLE 1. VISUAL REACTION TIME (RT) AND MOVEMENT TIME (MT) (IN MS) IN PATIENTS WITH PARKINSON'S DISEASE

		Left hand		*Right hand*	
Subject	*Age (yrs)*	*Pron. RT/MT*	*Supin. RT/MT*	*Pron. RT/MT*	*Supin. RT/MT*
01-JW	71	307/95	260/110	287/166	289/169
02-JB	41	640/162	498/164	627/181	677/314
03-WB	57	379/53	328/42	— —	— —
04-GB	70	563/109	467/90	544/91	422/128
05-RB	57	318/180	354/130	378/107	331/138
06-ON	68	279/230	327/85	— —	— —
10-JC	69	333/53	330/57	— —	— —
12-BW	72	450/71	530/68	568/61	506/60
13-BD	63	339/81	405/84	476/88	433/104
14-NS	54	242/64	312/87	391/59	369/66
15-GF	50	190/53	215/63	207/53	220/63
16-DC	60	470/71	273/68	379/60	301/53
17-WH	57	304/64	321/47	348/75	315/52
18-HH	63	464/158	651/349	398/120	678/97
19-PL	53	297/76	337/68	280/143	479/329
21-RL	65	445/53	433/46	521/58	553/69
23-AF	63	252/62	276/78	260/39	337/37
24-MP	63	506/104	419/85	378/93	467/109
27-MR	58	273/80	261/63	336/72	548/72
30-RL	38	318/129	368/89	323/103	306/147
31-FV	71	433/246	527/199	487/108	441/98
32-HG	72	277/144	274/148	403/60	362/63
33-AM	72	304/86	356/64	374/76	372/97
35-LG	62	517/85	501/121	423/65	359/60
36-AW	57	331/92	368/97	278/64	316/78
37-WA	48	511/66	413/84	402/87	451/96
38-PG	61	— —	— —	364/38	563/50
39-PG	53	579/239	548/236	345/277	419/224
40-JD	54	347/287	357/167	481/224	964/806

TABLE 2. VISUAL REACTION TIME (RT) AND MOVEMENT TIME (MT) IN ELDER CONTROL SUBJECTS (AGES 52 TO 80 YEARS)

		Left hand		*Right hand*	
Subject	*Age (yrs)*	*Pron. RT/MT*	*Supin. RT/MT*	*Pron. RT/MT*	*Supin. RT/MT*
01-BF	75	342/76	491/62	581/55	528/59
02-HP	72	301/56	296/49	287/54	265/55
03-RS	71	263/56	319/56	258/48	241/56
04-JL	75	389/52	382/61	315/48	318/52
05-MS	64	227/51	261/53	278/53	247/49
06-PB	60	267/71	295/62	342/98	288/65
07-AF	65	303/66	304/64	446/53	273/64
08-CE	71	— —	— —	401/45	463/58
09-CB	70	— —	— —	306/67	330/72
10-MW	61	330/89	323/76	360/66	321/79
11-LP	64	219/54	272/58	224/51	212/62
12-RR	57	213/46	235/47	267/54	265/45
13-MK	68	214/50	237/62	217/42	253/59
14-MF	52	249/51	260/49	251/67	291/55
15-DS	62	293/75	291/58	325/56	399/54
16-JB	60	237/69	268/58	273/60	260/65
17-KE	70	221/59	219/58	230/55	223/57
18-CU	80	496/101	474/71	445/80	400/63
19-HU	71	290/50	304/59	280/45	317/53
20-KS	70	272/79	314/60	453/84	476/58
21-JS	71	251/54	270/67	277/62	258/52

TABLE 3. VISUAL REACTION TIME (RT) AND MOVEMENT TIME (MT) IN YOUNGER CONTROL SUBJECTS (AGES 20 TO 45 YEARS)

		Left hand		*Right hand*	
Subject	*Age (yrs)*	*Pron. RT/MT*	*Supin. RT/MT*	*Pron. RT/MT*	*Supin. RT/MT*
01-DC	41	233/68	331/46	246/63	249/64
02-HT	39	191/40	188/32	223/33	198/32
03-RM	24	258/47	193/48	245/50	236/42
04-PW	22	228/80	234/53	258/59	238/65
05-BG	20	276/45	396/43	246/36	271/37
06-TT	38	260/55	276/41	294/53	242/50
07-AS	22	189/50	204/44	201/41	204/46
08-DB	23	237/48	206/34	217/46	217/45
09-MH	23	269/71	275/68	270/56	270/54
10-EM	45	306/71	323/75	418/62	352/69
11-RP	22	223/52	227/43	315/41	263/46

the variability of motor function which makes pathophysiological studies of parkinsonism so difficult and at the same time so interesting. We will first present visual RT results and then consider kinæsthetic RT results. Each subject had 20 visual RT trials (10 supinations and 10 pronations), with the right hand and 20 trials with the left hand, making a total of 40 visual RT trials. Table 1 shows results from parkinsonians, Table 2 for the elder controls and Table 3 for the younger controls. In most cases 4 median RT and 4 median MT scores are given for each subject: RT and MT for supination and pronation on right and left. If all scores had been obtained for all the 29 parkinsonians, then there would have been 116 RT and 116 MT scores. For 4 patients, however, one hand could not be tested (due to tremor), and for this reason we obtained 108 RT and 108 MT scores for the 29 patients. For the 21 elderly controls, there should have been 84 RT and 84 MT scores, but 4 RT and MT scores were lost due to malfunction of apparatus. The expected numbers of 44 RT and 44 MT scores were obtained in the 11 younger controls.

Comparisons of the scores for the three groups of subjects (Table 4) yielded the expected finding that RT and MT are slowest in parkinsonism, intermediate in elder control subjects, and fastest in younger control subjects, with all of these differences being statistically significant ($P < 0.01$, Mann-Whitney U Test). But within the parkinsonian group there were large variations (not only between subjects, but between hands of the same subject and even between supination and pronation for the same hand), and in what follows we will examine the wide range of performance within the parkinsonian group with the aim of answering certain questions relating to the factors underlying the RT and MT deficits in parkinsonism.

1. *Does RT Impairment Occur in the Absence of Bradykinesia?*

Table 4 shows that MT impairment is more severe than RT impairment in parkinsonism and this raises the question of whether parkinsonians would show any RT impairment at all without MT impairment. To answer this question we (1) selected the parkinsonian MTs at or below the median MT for the elder controls (58 ms), (2) selected the parkinsonian RTs occurring with these short parkinsonian MTs and (3), compared these parkinsonian RTs with the appropriate subset of the elder control RTs.

TABLE 4. GROUP MEANS AND MEDIANS FOR SIMPLE VISUAL RT

	Parkinsonians (*29*)		*Elder controls* (*21*)		*Younger controls* (*11*)	
	Mean	*Median*	*Mean*	*Median*	*Mean*	*Median*
Age	60.7	61.0	67.1	70.0	29.0	23.0
RT	399.2	370.5	308.0	287.5	254.5	245.5
MT	114.2	85.5	60.1	58.0	51.0	48.0

The figures in parentheses indicate the number of subjects in the category.

TABLE 5. RT IN PARKINSONIANS AND ELDER CONTROLS MATCHED FOR SHORT MT

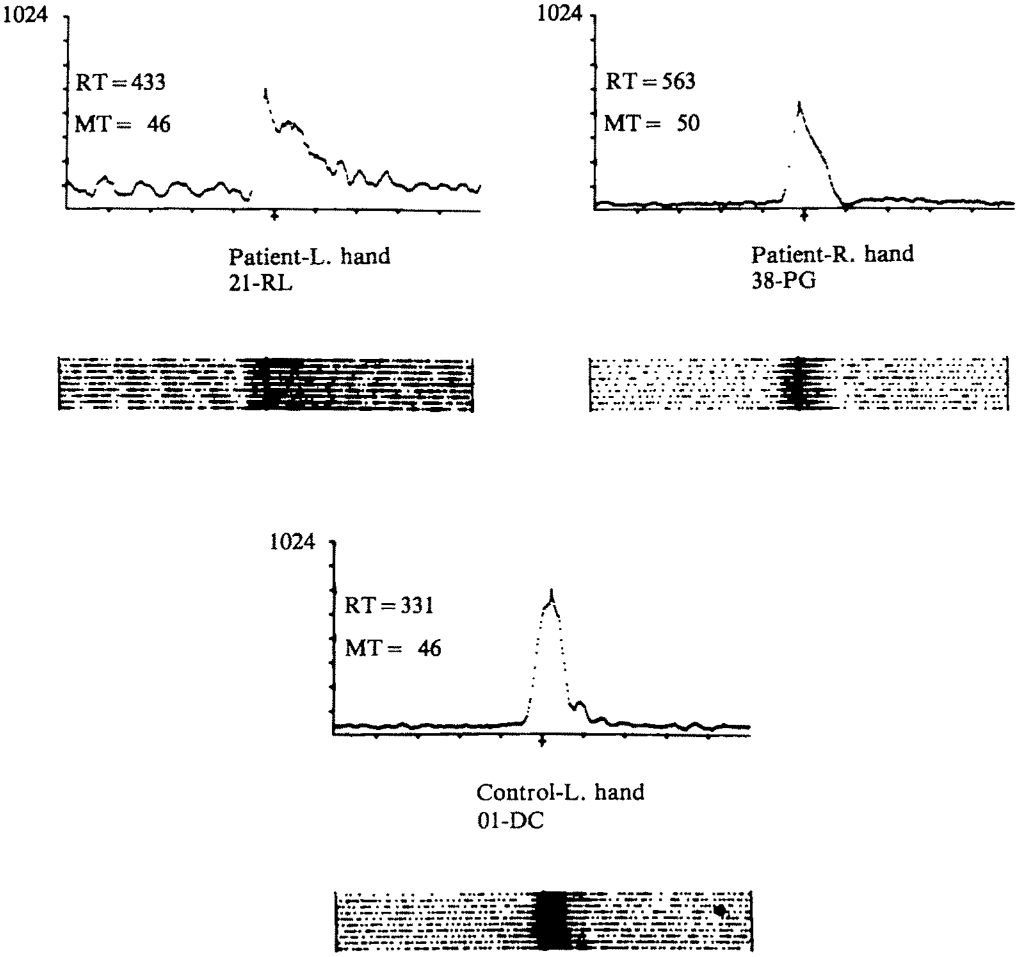
	Parkinsonians (16 scores)		*Elder controls (44 scores)*	
	Mean	*Median*	*Mean*	*Median*
MT	49.0	52.5	52.5	53.0
RT	351.7	331.5	293.4	267.5

Table 5 shows that these short parkinsonian MTs (16 MTs from 8 out of 29 patients) were well matched with the 44 elder control MTs at or below the elder control MT median: mean and median of the selected group of 16 parkinsonian MTs were 49.0 ms (mean) and 52.5 ms (median) as compared to 52.5 ms (mean) and 53.0 ms (median) in the 44 elder control MTs (from 17 out of 22 subjects) at or below the median of the elder control group. The RTs for these two subgroups, however, were significantly different: median RT in the subgroup of 16 parkinsonian RTs was 331.5 ms as compared to 267.5 ms in the corresponding elder control subgroup. This difference between the 16 parkinsonian RTs and the 44 elder control RTs was statistically significant ($P < 0.01$, Mann-Whitney U Test), with only 3 of the 16 parkinsonian RTs being at or below the median RT value for the elder controls. In conclusion, then, it is apparent that parkinsonians exhibit an impairment of RT even when the associated movement itself is of normal speed, and that RT impairment in parkinsonism can occur in the absence of bradykinesia.

Before leaving the matter of slowed RTs in parkinsonians with short MTs, it may be useful to consider the EMG pattern associated with the long RTs. Of the 16 parkinsonian RTs we have been considering, the longest was 563 ms in parkinsonian subject 38. Fig. 2 shows the EMG activity occurring with the movements associated with the RTs in this subject. Unlike the prolonged EMG rise-times occurring in parkinsonians with long MTs, the EMG rise-times for this patient with short MTs and long RTs were indistinguishable from those occurring in control subjects. A second such case is shown for Patient 21, who had an MT of 46 ms with an RT of 433 ms. This subject's EMG record (fig. 2) exhibited resting tremor, but the time from onset to peak of EMG discharge was normal. In conclusion, then, parkinsonian RT may be impaired even when the build-up of EMG activity occurs normally and when movement occurs with normal speed.

2. *Does Bradykinesia Occur in the Absence of RT Impairment?*

For the elder control group, median RT was 287.5 ms, and within the parkinsonian group 18 out of 108 RT scores were at or below this value. For this selected subgroup (Table 6) of 18 parkinsonian RT scores (in 10 out of 29 patients), RT values of 256 (mean) and 267 (median) were well matched with RT values of 250 (mean) and 256 (median) for the 40/80 elder control RT scores at or below the median for the elder controls. But in spite of this good match between RTs in these selected parkinsonian and elder control subgroups, MTs in the subgroups were different: MT scores were 94 (mean) and 66 (median) in the parkinsonian subgroup as compared to 56 (mean) and 55 (median) in the corresponding elder control subgroup. The difference between the subgroups was statistically significant



Patient-L. hand
21-RL

Patient-R. hand
38-PG

Control-L. hand
01-DC

Fig. 2. Electromyographic records of patients with long RTs with short MTs. For each subject there are two forms of displays: the rows of dots (rasters) in each display correspond to amount of rectified EMG. Since each row corresponds to a separate period of EMG, the raster provides a compact display of variability and other EMG features which may be lost in averages, shown above each raster. Above each raster is the average EMG amplitude for the set of individual trials depicted in the rasters. The ordinate scale for the averages gives rectified biceps EMG amplitude in microvolts. The full time span of rasters and averages is 2 s, with each of the small time marks below the average corresponding to 200 ms. The central line in rasters and the central arrow in the averages correspond to detection of handle displacement beyond the 5 deg zone in which the handle was held prior to the RT movement. Two parkinsonians (Table 1: 21-RL and 38-PG) with MTs shorter than the median MT of the control group exhibited normally brisk biceps EMG characteristic of rapid ballistic supination, but these subjects nevertheless exhibited abnormally long RTs. Typical EMG in control subject (Table 2: 01-DC) is shown for comparison below.

TABLE 6. MT IN PARKINSONIANS AND ELDER CONTROLS MATCHED FOR SHORT RT

	Parkinsonians (18 scores)		*Elder controls (40 scores)*	
	Mean	*Median*	*Mean*	*Median*
RT	255.8	267.0	249.8	255.5
MT	94.5	66.0	56.2	55.0

($P < 0.05$, Mann-Whitney U Test). The discrepancy between mean and median (94 ms *versus* 66 ms) in the parkinsonian subgroup reflects the performance of several patients having MTs which were quite long even with reasonably fast RTs. These patients were Nos. 1, 6 and 32. The scores of Patient 32 are listed in Table 7, which shows that for the left hand both of this patient's RTs were shorter than the median RT for the elder controls', while the associated MTs for this same left hand (144 and 148 ms) were longer than the longest MT (101 ms) within the entire set of 80 MT scores for elder controls. It is thus apparent that marked bradykinesia (that is, abnormally slow voluntary movement) can occur in the absence of RT impairment. Patient 32 is also of note in connection with the striking differences between the two arms, which were, incidentally, clinically obvious. Thus, for the right arm MT was short and RT was long. The EMG patterns typical of the bradykinetic parkinsonian movements are illustrated in fig. 3: there is a reciprocal change in muscle activity for the reciprocal movements studied—but with the rates of change in muscle activity being abnormally slow for both increases and decreases of EMG activity with the two directions of movement.

Before leaving this consideration of relation of MT and RT, it is to be noted that while the correlation of MT and RT was statistically significant in all three groups, the strength of the correlation between RT and MT was considerably greater within the parkinsonian group as a whole ($r = 0.525$, df = 106, $P < 0.01$) than in the elder control group ($r = 0.328$, df = 78, $P < 0.01$) or the younger control group ($r = 0.349$, df = 42, $P < 0.05$). The existence of the stronger correlation within the parkinsonian group means that, in general, RT impairments become more severe as bradykinesia becomes more severe, and *vice versa*. However, the fact remains that in

TABLE 7. MEDIAN SCORES SHOWING DISSOCIATION OF RT AND MT WITHIN A SINGLE PARKINSONIAN SUBJECT

	Left		*Right*	
	Pron.	*Supin.*	*Pron.*	*Supin.*
RT	277	274	403	362
MT	144	148	60	63

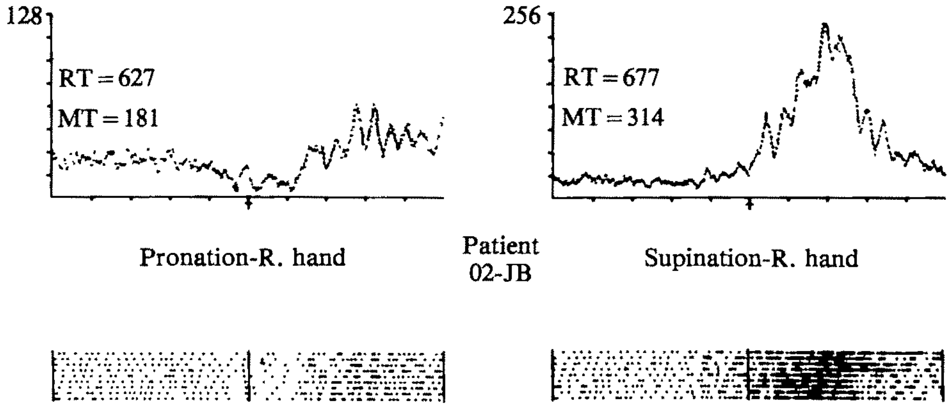


FIG. 3. Slow EMG changes associated with bradykinesia. The records above show reciprocal biceps inactivity (with pronation, *left*) and activity (with supination, *right*) in a subject (Table 1: 02-JB) exhibiting marked prolongation of both RT and MT. Note that the EMG rise and fall times are abnormally long. Time scale and other features of these displays are given in legend for fig. 2.

spite of this correlation, there may be striking instances of dissociation between RT and MT impairments within the parkinsonian group. In these respects the relationship between MT and RT seems similar to other distinct features of Parkinson's disease, such as tremor and rigidity, which tend to increase as the disease progresses, but which may be quite disparate in individual patients.

3. *Do Parkinsonian Patients have Selective Impairments of Kinæsthetic Reaction Time?*

The previous results in this report involved RTs and MTs triggered by visual stimuli. In this section we report on RT studies in which the triggering GO stimulus was handle displacement produced by the torque motor (fig. 1). In this kinæsthetic RT paradigm the READY and DIRECTION (pronation or supination) signals were visual stimuli delivered simultaneously (as in the visual RT paradigm), but the GO signal was a handle displacement produced by the torque motor. There were four possible combinations of the two possible visual DIRECTION signals and the two possible kinæsthetic GO signals.

Visual DIRECTION Signal	*Kinæsthetic GO Signal*
Pronate	Pronation
Pronate	Supination
Supinate	Pronation
Supinate	Supination

Subjects received 32 trials with each arm (8 trials for each of the four combinations).

For visual RT, RT had been scored as the time from GO to the initial displacement of the handle, but for kinæsthetic RT this scoring procedure was not possible since the GO signal itself displaced the handle. For this reason only a single kinæsthetic RT performance measure was obtained: the time from kinæsthetic GO stimulus to completion of the 45 deg pronation or supination movement. We will use the term kinæsthetic RT in reference to this time, keeping in mind that the kinæsthetic RT value we obtained actually corresponds to the sum of RT and MT in the visual RT paradigms.

Tables 8, 9 and 10 show median kinæsthetic RT scores for the parkinsonian and for the elder and younger control subjects considered in the previous sections of this

TABLE 8. KINÆSTHETIC REACTION TIME IN PARKINSONIANS

		Left hand		*Right hand*	
Subject	*Age (yrs)*	*Pron. P-P/P-S*	*Supin. S-S/S-P*	*Pron. P-P/P-S*	*Supin. S-S/S-P*
01-JW	71	382/430	380/388	530/609	572/497
02-JB	41	563/644	581/692	600/950	867/1224
03-WB	57	353/460	337/374	407/640	558/470
04-GB	70	255/499	240/420	209/620	249/555
05-RB	57	276/488	332/372	342/385	362/393
06-ON	68	442/554	440/443	385/449	466/438
10-JC	69	254/323	278/402	— —	— —
12-BW	72	246/351	268/334	280/586	299/362
13-BD	63	285/577	371/494	362/529	470/475
14-NS	54	289/308	289/344	347/414	311/351
15-GF	50	211/240	271/262	227/262	277/269
16-DC	60	297/365	315/329	288/353	258/345
17-WH	57	272/283	314/363	249/409	333/402
18-HH	63	684/815	873/197	517/839	694/790
19-PL	53	578/484	495/518	797/501	675/817
21-RL	65	581/483	410/503	409/610	649/626
23-AF	63	228/256	231/283	227/241	245/244
24-MP	63	297/425	293/356	427/517	318/437
27-MR	58	250/310	285/287	282/327	269/268
30-RL	38	546/597	387/576	574/649	414/555
31-FV	71	571/681	639/826	552/630	535/656
32-HG	72	315/401	460/503	328/359	338/394
33-AM	72	334/529	347/329	595/460	398/595
35-LG	62	371/524	499/505	495/499	393/456
36-AW	57	306/377	368/367	264/330	304/294
37-WA	48	307/488	381/495	540/547	503/752
38-PG	61	— —	— —	360/503	350/393
39-PG	53	371/460	350/470	455/576	322/506
40-JD	54	— —	— —	— —	— —
Mean		365/458	386/423	409/511	423/502
Median		307/460	350/388	385/503	362/456

TABLE 9. KINÆSTHETIC RT IN ELDER CONTROLS (AGES 52 TO 80 YEARS)

		Left hand		*Right hand*	
Subject	*Age (yrs)*	*Pron. P-P/P-S*	*Supin. S-S/S-P*	*Pron. P-P/P-S*	*Supin. S-S/S-P*
01-BF	75	276/693	310/493	254/276	258/266
02-HP	72	504/426	487/451	506/372	549/498
03-RS	71	237/400	310/295	305/324	286/357
04-JL	75	260/342	346/339	322/382	307/429
05-MS	64	234/570	239/364	260/482	270/466
06-PB	60	264/388	266/414	290/430	347/305
07-AF	65	222/282	229/313	234/308	240/296
08-CE	71	— —	— —	260/422	223/329
09-CB	70	— —	— —	484/690	495/563
10-MW	61	314/441	396/346	338/475	307/503
11-LP	64	263/310	381/379	314/373	250/339
12-RR	57	212/216	204/222	261/234	209/214
13-MK	68	232/250	259/300	226/254	205/253
14-MF	52	246/316	227/316	264/344	233/370
15-DS	62	236/532	287/459	371/439	247/430
16-JB	60	286/388	341/357	347/438	362/414
17-KE	70	226/217	220/243	253/264	212/230
18-CU	80	278/378	254/313	254/389	319/407
19-HU	71	234/408	256/337	246/323	237/292
20-KS	70	393/321	342/433	349/352	254/440
21-JS	71	246/449	281/375	251/511	423/638
Mean		272/386	297/355	304/385	297/383
Median		246/388	281/346	264/373	258/370

TABLE 10. KINÆSTHETIC RT IN YOUNGER CONTROLS (AGES 20 TO 45 YEARS)

		Left hand		*Right hand*	
Subject	*Age (yrs)*	*Pron. P-P/P-S*	*Supin. S-S/S-P*	*Pron. P-P/P-S*	*Supin. S-S/S-P*
01-DC	41	216/238	240/220	236/252	220/252
02-HT	39	199/196	195/188	200/192	179/189
03-RM	24	200/267	195/220	242/235	184/242
04-PW	22	209/267	215/228	234/260	225/224
05-BG	20	226/250	186/229	216/214	220/220
06-TT	38	210/356	225/242	216/330	254/257
07-AS	22	220/231	227/234	216/219	205/225
08-DB	23	215/238	198/231	213/219	208/231
09-MH	23	241/289	365/376	245/262	268/252
10-EM	45	249/398	276/332	274/352	261/307
11-RP	22	211/282	221/272	244/279	227/230
Mean		218/274	231/252	230/256	223/239
Median		215/267	221/231	234/252	220/231

report, and Table 11 summarizes the data in these Tables and also compares kinæsthetic and visual RT in the three groups. As with the results already reported for visual RT, kinæsthetic RT scores were slowest in parkinsonians, intermediate in elder control subjects, and fastest in younger control subjects. However, the magnitude of the kinæsthetic RT difference between patients and elder controls was less than the magnitude of the visual RT difference between patients and controls. Thus Table 11 shows that in the parkinsonian group median visual RT plus MT was 456 ms, while the corresponding score for the controls was 346 ms, a difference of 110 ms. For kinæsthetic RT, the median for the patients was 396 ms as compared to 308 ms for the elder controls. Thus, parkinsonian and elder control scores were somewhat closer for kinæsthetic RT than for visual RT and MT. In contrast, the magnitude of the kinæsthetic RT difference (78 ms) between elder and younger control medians was greater than the magnitude of the visual RT and MT difference between the elder and younger controls (52 ms). As already pointed out, kinæsthetic RT measure really corresponds to the sum of visual RT and MT, and so it seemed appropriate to sum visual RT and MT to obtain a performance measure to compare with kinæsthetic RT. It is the results of this summation which are shown in Table 11.

TABLE 11. GROUP MEANS AND MEDIANS FOR KINÆSTHETIC RT AND FOR SUMS OF VISUAL RT PLUS MT IN PARKINSON'S DISEASE AND IN ELDER CONTROLS AND YOUNGER CONTROLS

	Parkinsonians	*Elder controls*	*Younger controls*
	Kinæsthetic/Visual RT + MT		
Mean	435/513	332/368	240/305
Median	396/456	308/346	230/294

4. *What is the Effect of the Direction of Triggering Displacement on Kinæsthetic RT in Parkinsonism?*

One of the major factors motivating us to study kinæsthetic RT in parkinsonism was the belief that the direction of a limb displacement might be a more important determinant of kinæsthetic RT in parkinsonians than in control subjects. This premise was based on the observation of Tatton and Lee (1975) that long (50 ms) latency responses to muscle stretch are exaggerated in Parkinson's disease. Given this finding, it seemed possible that kinæsthetic RT in parkinsonism might be selectively impaired if the enhanced reflex muscle response elicited by the triggering displacement opposed the voluntary muscle response of the subject. It is to be noted that the reflex response to an externally produced limb displacement in a given direction is a movement in the opposite direction (for example, a reflex supination will occur in response to an externally produced pronation and an externally produced supination will evoke a reflex pronation). If parkinsonians were to have sufficiently exaggerated long-latency stretch reflexes, then their kinæsthetic RTs might be more impaired when a voluntary movement in one direction (for example, pronation) was triggered by a displacement in the same direction (also pronation). In such a case the reflex response to the displacing pronation would be supination, which would hinder the voluntary pronation response the subject was set to make.

TABLE 12. EFFECTS OF SAME OR OPPOSITE TRIGGERING DISPLACEMENTS ON KINÆSTHETIC RT IN PARKINSON'S DISEASE AND ELDER AND YOUNGER CONTROLS

	Parkinsonians	*Elder controls*	*Younger controls*
	Same/Opp	*Same/Opp*	*Same/Opp*
Mean	396/474	293/378	226/255
Median	352/460	262/371	220/240
SD	144/165	78/102	31/49

Our experimental observations failed to support this hypothesis. Table 12 gives kinæsthetic RT results broken down according to whether the reflex elicited by the triggering GO displacement was the same as, or opposite to the voluntary muscle discharge which the subject was set to make. The results in the patients were the converse of what we expected: their kinæsthetic RTs were relatively longer when the triggering displacement opposed movement than was the case for the elder or younger control subjects. The fact that the patients gave results opposite to those anticipated may actually have a rather trivial explanation. According to our hypothesis, displacements which opposed a given voluntary movement might actually have shortened kinæsthetic RT by causing reflex discharge in the agonist muscles which the patient was set to discharge voluntarily. However, it is also true that such an opposing displacement would require *more* muscle activity (to overcome the opposing torque) and that unless the reflex response were quite strong (as, for instance, in a patient with spasticity), then any shortening of kinæsthetic RT (which includes MT) due to the reflex response would be lost due to the need for increased muscular activity to overcome an opposing torque during movement. It has already been seen (fig. 3) that many parkinsonians with bradykinesia had very prolonged rise-times of EMG in the visual RT paradigm, and it appears that this factor may have given rise to the results obtained in our kinæsthetic RT paradigm. Table 12 shows that median kinæsthetic RT was 108 ms shorter when the displacement assisted as compared to opposed the movement, while the corresponding differences for the elder and younger control subjects were 109 and 20 ms, respectively.

5. *Is Choice Reaction Time Selectively Impaired in Parkinson's Disease?*

Since the time of Donders, differences in simple reaction time (SRT) and choice reaction time (CRT) have been used in studies of information processing by the central nervous system. Comparisons of CRT and SRT for subjects in different age groups have shown that CRT impairments are greater than SRT impairments in elderly subjects (Welford, 1958; Birren, 1964; Simon, 1967), and we have extended CRT-SRT comparisons to parkinsonian patients. In our SRT paradigm (*see Methods*), the READY signal and the DIRECTION (pronation or supination) signal came on simultaneously, and there was then a 2 to 4 s delay prior to the GO signal. The subjects thus had 2 to 4 s to 'get set' for the required motor response. In our CRT paradigm the READY signal came on by itself and then after a 2 to 4 s delay the DIRECTION and GO lamps came on simultaneously. For the CRT trials, subjects had no way to get set for a specific direction of movement prior to the GO signal. If there were a selective impairment in the speed of formulating or assembling a 'central motor program' in parkinsonism, then CRT should be selectively impaired in parkinsonian patients.

Observations on CRT and SRT were obtained from a different group of parkinsonian subjects than those described in parts 1 to 4 of this report. Subjects had 32 SRT trials followed by 32 CRT trials with one arm, and then 32 SRT followed by 32 CRT trials with the other arm. Each block of 32 trials involved 16 pronations and 16 supinations, with the directions of successive individual movements varying unpredictably.

Table 13 gives the median CRT and SRT scores for the 23 parkinsonians studied. Each patient could have been assigned 4 SRT scores (R Supin., R pron., L Supin., L pron.) and 4 corresponding CRT scores, but in several cases one or the other arm was not tested, leading to some omissions in the table. Table 13 also shows the differences between scores for CRT and SRT for a particular hand and direction of movement. For the entire set of CRT scores shown in Table 13, the median was 458 ms and the mean was 507, as compared to 397 median and 433 mean for SRT. These differences in CRT and SRT in our sample of parkinsonians were so slight that it did not seem warranted to pursue the hypothesis that such patients exhibit a selective impairment of CRT. It was for this reason that we did not obtain observations on CRT in a group of elderly control subjects. In the absence of control scores, however, we can cite several previous studies in normal subjects which have shown that CRT exceeds SRT by considerably more than the difference (61 ms median, 74 ms mean) which we observed in parkinsonians. The results of these studies will be given in the Discussion.

DISCUSSION

The results which have been presented demonstrate that speed of movement and speed of response initiation may be independently impaired in Parkinson's disease, even in the same patient in comparisons between the two limbs. Thus, a patient may exhibit impaired RT and normal MT with one arm and impaired RT with normal MT in the other. The failure of a number of previous studies to find an RT impairment in parkinsonism deserves comment, since this failure might seem to conflict with the results which we report. Thus, Talland (1963) found no significant

TABLE 13. SIMPLE REACTION TIME [SRT] AND CHOICE REACTION TIME [CRT] IN PARKINSON'S DISEASE

		Left hand		*Right hand*	
Subject	*Age (yrs)*	*Pron. SRT/CRT*	*Supin. SRT/CRT*	*Pron. SRT/CRT*	*Supin. SRT/CRT*
02-WH	72	818/399	568/414	518/445	533/459
03-AM	72	454/564	396/579	— —	— —
04-EH	56	365/427	334/404	418/419	470/402
05-RR	63	292/424	300/422	— —	— —
06-SD	52	408/437	336/432	318/458	366/424
07-PK	62	254/320	272/305	— —	— —
09-TG	45	499/716	523/619	389/739	397/704
11-GF	50	228/279	240/284	319/351	270/338
12-EC	72	606/697	637/612	435/556	542/784
13-AT	74	— —	— —	397/438	369/528
14-JS	64	383/458	563/548	434/473	408/526
15-MJ	60	518/683	561/786	629/686	546/572
17-BW	70	435/654	456/700	783/867	650/722
18-RM	41	215/261	220/288	277/296	256/316
19-CS	64	— —	— —	394/481	447/523
21-ST	51	498/457	580/458	433/423	476/422
24-RF	74	— —	— —	1070/930	925/1030
25-MK	53	344/494	444/549	423/528	526/511
29-PL	53	217/375	224/398	218/482	219/456
30-DR	57	275/500	281/492	334/551	326/527
31-JW	71	336/402	322/378	350/369	356/375
34-HG	72	329/457	324/311	394/456	350/330
35-VY	63	535/670	739/748	645/647	688/624
Mean	61	400/484	416/486	459/530	456/529
Median	63	374/457	366/445	408/477	428/517

All scores:		*SRT/CRT*
	Mean	433/507
	Median	397/458

RT differences between a group of ambulatory parkinsonian patients and age-matched controls; only that one-third of the patients rated as severely incapacitated (that is, very bradykinetic) was reliably slower. In another study (King, 1959), it was reported that in parkinsonism 'The time taken to initiate a response is virtually normal'. Schwab, Chapetz and Walker (1954) also found RT to be normal. Other studies have shown, in general, that parkinsonian RT is about 30 per cent longer than that of age-matched normal subjects and that there are large variations; some parkinsonians are quite slow, whereas others have normal RT (Cassell, Shaw and Stern, 1973; Evarts, Teräväinen, Beuchert and Calne, 1979; Flowers, 1976; Heilman, Bowers, Watson and Greer, 1976; Potvin and Tourtelotte, 1975; Velasco and Velasco, 1973). The most likely explanation for these differences lies in the wide range of symptomatology which can exist within any group of parkinsonians, and even within a single subject at different times in a single day. Thus, we did not observe that RT impairment occurs in all parkinsonian patients, and it seems clear that when bradykinesia is present it contributes to the magnitude of the RT impairment. However, our data clearly show that *some* patients exhibit RT impairment as an independent manifestation of a central motor disorder, and that this RT impairment need not be merely a consequence of bradykinesia. Another factor which must be kept in mind is the possibility of differences in the severity of the disorder in patients in our group and in the groups of these previous investigators. Diverse patient groups may differ greatly in the degree of illness, and since it is virtually impossible to have comparable severity of illness across different studies, it does not seem surprising that RT impairments have been detected in some studies and not in others. Patients in our study had been referred because of problems in therapeutic management, and therefore represented a category of moderate to severe motor deficits.

While showing clear impairments of simple RT, the patients in our study failed to exhibit selectively greater disturbance in any of the other RT tests which were administered. Thus, we found that median choice RT (CRT) was only 61 ms longer than simple RT (SRT), a difference which is actually less than differences between CRT and SRT in many previous reports on studies of normal subjects. Suci, Davidoff and Surwillo (1960) found that in old subjects there was an increase of more than 200 ms in CRT as compared to SRT. Talland (1965, pp. 526–561) studied SRT and CRT in a two-choice test with light signals and observed that CRT increases steeply in the seventies. Table 14 summarizes Talland's results.

TABLE 14. NUMERICAL DATA INFERRED ON BASIS OF FIG. 1 FROM TALLAND (1965)

Age	*SRT*	*CRT*	*Difference*
55	290	375	85
70	310	420	110
80	320	550	230

There has been some debate as to whether the increase in CRT in ageing is *disproportionately* greater than the increase of SRT. Botwinick (1973) discusses this matter as follows: 'As the RT situation becomes more complex and requires more difficult choice, responses become slower. The question is this: is there anything unique in the slow responses seen in the complex choice situations that is not set down or determined by RT in the simple situation? The old are slower than the young in the simple situation, and they are even more so in the complex situation—is there anything unique in their slowness of making choices that is not determined by their slowness in making simple responses to a simple stimuli?' As Botwinick goes on to point out, the matter seems to hinge on how one defines 'disproportionate'. It is beyond the scope of this article to review these observations on the nature and basis of CRT changes with ageing. The reader is referred to several excellent reviews on the subject by Botwinick (1973), Birren (1964) and Welford (1962). The differences between CRT and SRT obtained in the present study do not exceed differences reported for healthy older subjects, and CRT *per se* does not appear to be selectively impaired in parkinsonism.

The failure of the CRT studies to reveal selective impairment was unexpected; we had thought that CRT tests might provide a more sensitive index of a deficit in ability to select or formulate 'central programs'. Of course, our failure to detect selective impairment in a more complex task may merely have resulted from the fact that the type of motor performance which was required in our CRT tests was itself too simple. Thus, the CRT test in the present study was one in which displacement, velocity, and accuracy did not have to be precisely controlled by the subject. A disturbance might have emerged if our CRT test had involved a tracking task in which the accuracy, magnitude, and velocity of the movement had to be programmed following the delivery of the GO stimulus. In our studies it was only *direction* that had to be chosen. The observations of Flowers (1978*a*, *b*) indicate that different motor tasks might indeed reveal selective impairments of motor programming in parkinsonism. Certainly, our failure to find a selective impairment of CRT should not be taken as an indication that parkinsonians have no disorder in the ability to call up motor programs. Instead, we believe that our results point to the need for more carefully designed studies in which other features of movement (for example, amplitude, velocity, and accuracy) must be programmed.

Movement Time

Of the various measurements in the present study, movement time appears to be the one which is most profoundly and consistently affected in parkinsonism. Recordings of EMG activity indicated that the bradykinesia was the result of a failure of the agonist muscle to exhibit the abrupt build-up of discharge which normally occurs in ballistic movements. Abnormally high levels of EMG co-contraction in agonist and antagonist muscles prior to and during movement (a possible correlate of rigidity) was *not* a factor in the bradykinesia of our subjects. Rigid patients had the capacity to make abrupt movements and a number of the bradykinetic subjects were not rigid.

Slowing of movement occurs in normal ageing as well as in Parkinson's disease, and prolonged MT with ageing has at times been discussed in terms of a choice of accuracy over speed. Thus, Welford (1958) states that 'Where there is a choice open to them, older subjects appear rather consistently to shift the balance between speed and accuracy towards the latter. This has the effect of conserving action in the sense that less is wasted making the correcting errors. Such stress on accuracy does not, however, seem to be designed to conserve *energy* but rather to keep down the time taken to control action and make decisions. Since this time lengthens with age, we can see the care, caution, and accuracy manifested by older people as likely to maximize their overall achievement and thus as a very reasonable and sensible course to adopt. Whether the choice is deliberately taken is another matter: almost certainly it is not in each individual performance, although perhaps if we could trace back in a man's or woman's history we should find them having consciously built up habits which have in the course of time become generalized and deeply ingrained so that they are used without any awareness of doing so'. Although speculative, this teleological argument might perhaps also be applied to patients with Parkinson's disease.

Further support for the idea of a shift towards accuracy comes from the work of Salthouse (1979) on effects of age on the speed-accuracy trade-off. While it is possible that greater emphasis on precision might be a factor in contributing to lengthened MT and RT in parkinsonism, the existence of striking unilateral impairments of movement speed (fig. 4) indicates that in addition to any general shift in movement strategy in parkinsonism, there is a localized (at least to a given hemisphere) failure of systems functioning to provide the outputs underlying high-velocity movements.

Indices of Motor Impairment in Parkinson's Disease

Objective indices of motor impairment in parkinsonism may be useful from two standpoints: (1) they may help to clarify the nature of the central pathophysiological disturbance; (2) they may be of value in assessing the effectiveness of therapy. While RT studies may be useful in providing insights into the central disorder in parkinsonism it appears unlikely that the relatively slight RT impairments occurring in Parkinson's disease will be of value in assessing therapeutic efficacy.

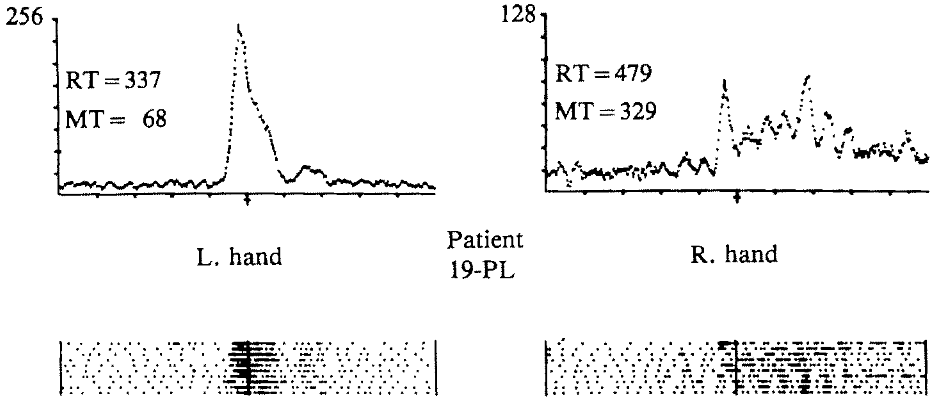


FIG. 4. Unilateral impairment of movement speed. This subject (Table 2: 19-PL) exhibited characteristically slow build-up of EMG activity with right-sided movements and normal build-up with left-sided movements. In addition, R hand EMG showed action tremor. Time and ordinate scales are the same as for fig. 2.

The changes in MT are more highly correlated with the clinical status than changes in RT, and if one is seeking an objective measure to use in assessing therapy, then the RT score has little to offer. It is possible, however, that while failing to reflect beneficial effects of treatment, RT impairment due to drug action may in some cases provide an indicator of adverse effects due to sedation. Impairment of RT in patients exhibiting improved MT was observed in a recent study of the actions of the dopamine agonist lisuride (Gopinathan, Teräväinen, Dambrosia, Ward, Sanes, Stuart, Evarts and Calne, 1981). In this context it is of interest to note the observation of Velasco and Velasco (1973) on effects of L-Dopa on RT and MT. In studies of 20 parkinsonian patients it was observed that administration of L-Dopa was followed by improved RT in only two cases, while in all other cases RT remained unchanged or worsened. In contrast, movement speed was markedly improved by L-Dopa, with the effect being statistically significant ($P < 0.001$), and it was concluded that '. . . L-Dopa improves the clinical picture of Parkinson's disease by increasing the speed at which a body segment can be transferred in space. . . .'

SUMMARY

Both reaction time and movement time tend to be prolonged in Parkinson's disease, but they are often impaired independently of each other.

Prolongation of RT is relatively slight, while MT undergoes more substantial and consistent disturbance.

Choice RT and kinæsthetic RT do not have any advantage over simple visual RT as measurements of neurological deficit in parkinsonism, since they are all impaired to the same extent.

MT is more useful than RT as an objective indicator of therapeutic efficacy, but further studies of RT (with tests requiring programming of displacement, velocity, and accuracy) may provide insights into the nature of the central motor disorder in Parkinson's disease.

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AUTONOMIC NEUROPATHY IN EXPERIMENTAL ALLERGIC NEURITIS

AN ELECTROPHYSIOLOGICAL AND HISTOLOGICAL STUDY

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INTRODUCTION

EXPERIMENTAL allergic neuritis (EAN), which was first described by Waksman and Adams (1955), is an immunologically mediated disorder affecting the peripheral nerves of animals that have been injected with peripheral nervous tissue and adjuvants. The pathological changes are those of segmental demyelination with relative sparing of axons and infiltration by inflammatory cells (Waksman and Adams, 1955, 1956; Hall, 1967*a*; Allt, 1976). There is a striking resemblance of the clinical and pathological features of EAN to those of acute idiopathic polyneuritis (AIP: Landry-Guillain-Barré syndrome) (Arnason, 1975). There is considerable clinical and some histopathological evidence to suggest that the autonomic nervous system is involved in AIP (Birchfield and Shaw, 1964; Matsuyama and Haymaker, 1967; Lichtenfeld, 1971; Tuck and McLeod, 1978). Since a study of the autonomic nervous system in animals with EAN might provide an explanation for some of the clinical disturbances of autonomic function observed in patients with AIP and help in the understanding of its pathophysiology we have performed an electrophysiological and histopathological study of the vagus and greater splanchnic nerves of guinea pigs with EAN. No electrophysiological studies have been previously performed on the autonomic nervous system in EAN, and the pathological changes have received little attention.

METHODS

Animals

Adult guinea pigs of both sexes were used in the studies. Their ages ranged from 19 to 36 weeks and their weights from 540 to 870 g. Their diet consisted of medicated rabbit and guinea pig pellets and green vegetables.

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Induction of Experimental Allergic Neuritis

EAN was induced with a mixture of homogenized canine peripheral nerve and complete Freund's adjuvant. Fresh dog sciatic nerves were cleaned, weighed and cut into small pieces with a scalpel blade, homogenized with 0.9 per cent sodium chloride (1 ml/g of nerve), and centrifuged at 2,000 rpm for 10 minutes. The supernatant was thoroughly mixed with an equal volume of complete Freund's adjuvant and was used within 6 hours of preparation.

Each animal was given subcutaneous injections of 0.1 ml of antigen into the pads of both forefeet and into six sites on the trunk, and an intraperitoneal injection of 0.1 ml of pertussis vaccine. The animals were examined each day thereafter and were killed from 1 to 42 days after the onset of EAN. A control group of animals was matched for age with the experimental group but received no injections.

Motor Conduction Velocity

The velocity of conduction in the fastest conducting motor fibres of the right posterior tibial nerve was measured using a method similar to that described by Fullerton (1966). The animals were anæsthetized with 30 mg/kg intraperitoneal pentobarbitone sodium which was supplemented when necessary with ether. The stimulating cathodes consisted of two stainless steel hypodermic needles, the proximal of which was inserted just caudal to the ischial tuberosity and the distal into the medial side of the ankle. The anode was another needle inserted into the gluteal region approximately 5 mm cranial to the proximal cathode. A pair of needles was inserted into the muscles on the plantar aspect of the foot to record the evoked action potential in the small muscles; a ground electrode was inserted into the foot between the proximal recording electrode and the distal stimulating cathode. The nerve was stimulated at each site at a rate of once every 1.3 s with a stimulus of 0.05 ms duration and intensity of up to 90 V derived from an isolated stimulator (Devices, Mark IV) triggered by a Digitimer to obtain a maximal response from the muscle. The muscle action potentials were amplified by a preamplifier (Tektronix FM 122) and displayed on the upper trace of a dual-beam storage oscilloscope (Tektronix 5103 N). A millisecond time scale from the Digitimer was displayed on the lower trace. Permanent records of the display were made on Polaroid film. The animals were kept warm on a heated table and the temperature of the limb was recorded with a thermistor probe inserted into the back of the thigh, halfway between the two stimulating cathodes. The distance between the stimulating cathodes was measured after straightening the limb. The latencies were measured from the onset of the stimulus artefact to the onset of the initial negative deflection of the muscle action potential. Maximal motor conduction velocity was calculated by dividing the distance between the stimulating cathodes by the difference between the latencies.

Conduction in Vagus and Splanchnic Nerves

After measuring the motor conduction velocity, electrophysiological studies were performed *in vitro* on the left cervical vagus nerves of 14 guinea pigs with EAN and 9 controls, and on the left greater splanchnic nerves of 7 guinea pigs with EAN and 6 controls.

After killing the animals with ether, the vagus and splanchnic nerves were removed and placed on a gauze swab soaked in 0.9 per cent sodium chloride solution and any adherent soft tissue was carefully removed.

Recordings of the compound nerve action potentials were made with the nerve in a small perspex chamber (Hopkins and Lambert, 1972). There were nine parallel silver electrodes of 0.5 mm diameter, about 5 mm apart whose axes were at right angles to the long axis of the chamber. The cleaned nerve was carefully placed on the silver electrodes and was looped around the outer two. A small drop of 1 per cent xylocaine was placed on the nerve at the distal recording electrode supporting its most cranial end and the nerve was covered with warm (37° C) paraffin oil through which oxygen was slowly bubbled. The temperature of the paraffin oil was monitored continuously by a thermistor probe and maintained at 37.0 to 37.5° C by a bath of warm water surrounding the chamber. The stimulus was applied through the pair of electrodes at the caudal end of the nerve, and the action potential recorded through different pairs of recording electrodes.

The action potential was amplified by a solid state, low noise differential amplifier with a dual field effect transistor input. The common mode rejection was greater than 100 000 : 1 at 50 Hz and the input impedance at 1000 Hz was 970 MΩ. The output from this preamplifier was amplified, displayed and recorded in the same way as the muscle action potentials. The conduction velocity of the fastest fibres of each component of the compound action potential was calculated by dividing the distance between the stimulating cathode and the active recording electrode by the latency measured from the onset of the stimulus artefact to the onset of each negative component of the compound action potential. The amplitude of the action potentials was measured from baseline to peak. A calibration signal was derived from a 1.35 V mercury cell and a voltage divider. At the end of each experiment the interelectrode impedance was measured using a signal generator connected in series with a 10 MΩ resistance to provide a constant current source at 1 kHz. The voltage drop (E_1) was first measured across the recording electrodes with a Tektronix 5103 N oscilloscope, and then across a 1000 Ω resistance (E_2) from which the unknown impedance (Z) was calculated using the relationship $Z = E_1/E_2$, where Z is in kΩ. The duration of each action potential was measured from the onset of the negative potential to the point at which it returned to the isoelectric line.

The areas of the A-waves of the compound action potentials of the vagus nerves were measured by placing a sheet of transparent squared paper over the photographic record of the action potential and counting the number of 1 mm squares beneath the outline of the potential and above the baseline. The resulting time integral was expressed in mV/ms.

Histological Studies

For both light and electron microscope examination, tissues were fixed by perfusion with Karnovsky's solution followed by 2.5 per cent glutaraldehyde in 1/15 M phosphate buffer at 4° C. The right cervical vagus, left greater splanchnic and left sciatic nerves were dissected and 1 cm of each nerve was placed in 2.5 per cent glutaraldehyde solution for 24 hours, then in Dalton's solution for 1½ hours, 2.5 per cent uranyl acetate for 1 hour and then dehydrated in alcohol. For light microscopy, 0.5 to 1.0 μm sections were cut and stained with 1 per cent toluidine blue. Photomicrographs of three vagus and four splanchnic nerves from control guinea pigs with EAN were enlarged 1,000 times. The area of each nerve was measured by drawing its outline on to tracing paper which was cut out and weighed on a Mettler H54 balance. The area was calculated from the weight using a factor obtained by weighing a known area of paper. The diameter and the number of myelinated fibres were counted with a Zeiss TGZ3 particle size analyser which was used in the exponential mode in order to obtain a more accurate assessment of the distribution of small diameter fibres (Dyck, 1975). The total myelinated fibre density was calculated by dividing the total fibre count by the intraperineurial area and histograms showing the frequency of distribution of fibres of varying diameters were constructed. For electron microscopy, ultra-thin sections were cut with a glass or diamond knife and stained on copper grids with lead citrate and were examined with a Philips EM200 or 201 electron microscope. About 1 cm of nerve was fixed in buffered formalin, stained for 24 hours in 1 per cent osmium tetroxide and, after maceration for 24 hours in a solution of two parts glycerol to one part water, small groups of fibres and single fibres were separated by teasing (Visozo and Young, 1948; Thomas, 1955). The appearance of individual teased fibres was documented using the alphabetical classification of Dyck (1975).

Statistical Methods

Means are expressed with standard deviation and were compared using the two-tailed Student's t test. The difference between means was considered to be significant if $P \leqslant 0.05$.

Sample variances were compared using the variance ratio test (Snedecor's F test). If there was a significant difference between the variances ($P < 0.05$) the means were compared using t′ instead of t (Snedecor and Cochran, 1967).

RESULTS

Clinical Findings

Twenty-eight of 40 guinea pigs that were injected with the mixture of homogenized peripheral nerve and Freund's adjuvant and pertussis vaccine developed signs of EAN after a mean interval of seventeen days from the date of injection. Five of the animals were reluctant to walk and had a tendency to splay the hindlimbs, 15 had obvious weakness of the hindlimbs but were still able to move about the cage, and 8 were almost completely paralysed in all limbs. The animals were killed from one to forty-two days (mean 9; SD, 9) after the onset of weakness.

Electrophysiological Studies

Motor conduction. The mean distal motor latency in affected animals was 1.8 ms (range 0.94 to 3.17 ms; SD, 0.5) which was significantly greater than the mean value of 1.5 ms in control animals (range 1.00 to 1.83 ms; SD, 0.2) ($P < 0.05$). The mean motor conduction velocity in guinea pigs with EAN was 41 m/s (range 10.1 to 67.0 m/s; SD, 13) and was 84 per cent of the control value of 51 m/s (range 40.0 to 63.1 m/s; SD, 8). The difference is significant ($P < 0.01$). The mean hindlimb temperature in the guinea pigs with EAN was 35.2° C (SD, 1.3) and in the control group was 35.7° C (SD, 0.8). The difference is not significant. The muscle action potentials were dispersed in 10 of the 19 affected animals, in 7 of which motor conduction velocity was within the normal range. The results are summarized in Table 1.

Vagus nerves. There were two major components of the monophasic compound action potentials of the cervical vagus nerve of healthy guinea pigs. The first was the negative A-wave which contained two major peaks ($\alpha\beta$ and $\gamma\delta$; fig. 1A). The second

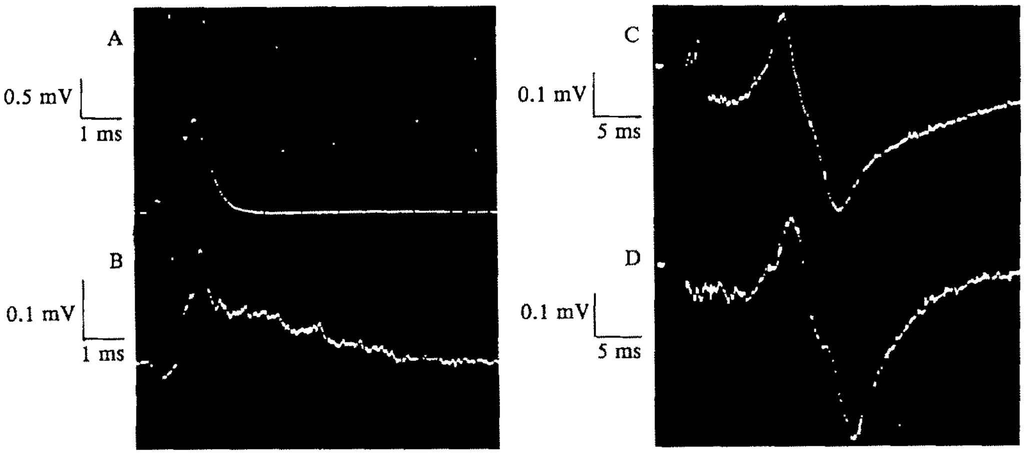

FIG. 1. Cervical vagus nerve compound nerve action potentials. A, A-wave recorded from a control nerve showing $\alpha\beta$ and $\gamma\delta$ deflections; B, A-wave recorded from a nerve from a guinea pig with EAN; the amplitude is much less than that of the control and there is marked temporal dispersion. C and D, biphasic C-waves recorded from a nerve from a control and a diseased animal, respectively.

TABLE 1. NEUROPHYSIOLOGICAL STUDIES IN EAN

	Sciatic nerve		*Vagus nerve*					*Splanchnic nerve*				
			A-wave			*C-wave*		*A-wave*			*C-wave*	
	Latency (ms)	*MCV (m/s)*	*CV (m/s)*	*Amplitude (mV)*	*Duration (ms)*	*CV (m/s)*	*Amplitude (μV)*	*CV (m/s)*	*Amplitude (μV)*	*Duration (ms)*	*CV (m/s)*	*Amplitude (μV)*
Control (n = 19) range	1.00–1.83	40.0–63.1	56–70	2.7–5.6	1.5–2.1	1.5–2.0	100–580	51–70	250–700	3.2–5.3	1.30–1.73	230–720
Mean	1.5	51	63	4.1	1.8	1.8	310	60	440	4.1	1.4	410
SD	0.2	8	5	0.9	0.2	0.2	180	7	150	1.1	0.2	200
EAN (n = 14) range	0.94–3.17	10.1–67.0	38–63	0.46–4.5	1.3–6.2	1.3–2.8	100–750	8–58	15–280	4.7–9.5	0.8–1.67	130–200
Mean	1.8	41	53	2.6	2.9	1.7	380	25	100	7.2	1.3	170
SD	0.5	13	6	1.3	1.5	0.4	220	20	90	1.6	0.3	30
	$P < 0.05$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.05$	$P > 0.05$	$P > 0.05$	$P < 0.01$	$P < 0.001$	$P < 0.01$	$P > 0.05$	$P < 0.05$

was the C-wave which was biphasic, the initial deflection being negative (fig. 1c). The A-wave was dispersed in 9 of the 14 vagus nerves from affected guinea pigs and the $\alpha\beta$ and $\gamma\delta$ peaks could not be distinguished (fig. 1b). By contrast the C components of the action potentials from the affected guinea pigs did not differ in configuration from the controls (fig. 1d). The values for the mean conduction velocity and amplitude of the A- and C-waves from control and affected guinea pigs are summarized in Table 1. In animals with EAN the conduction velocity of the A-wave was significantly slowed (84 per cent of control mean), the amplitude of the A-wave was significantly reduced, and its duration was significantly increased. The velocity and amplitude of the C-wave do not differ significantly in the two groups. The mean impedance between the recording electrodes for the control vagus nerves was 43 kΩ (SD, 11) and for the vagus nerves from affected guinea pigs was 44 kΩ (SD, 13). The difference is not significant.

The compound action potentials of 6 control vagus nerves and 9 vagus nerves from the affected guinea pigs were recorded from two successive active electrodes separated by 5 mm and the time integral of the A-wave recorded at the distal electrode was expressed as a percentage of that at the proximal electrode for each nerve. The mean ratio for the control nerves was 98 per cent (SD, 15) and from those of affected animals was 78 per cent (SD, 28). Although the mean ratios did not differ significantly the ratios of four nerves from affected animals were more than two standard deviations below the control mean.

Splanchnic nerves. The compound action potentials of the greater splanchnic nerves of the control guinea pigs contained an A-wave in which there were two smaller peaks (β and $\gamma\delta$) and B- and C-waves (fig. 2a and c). Temporal dispersion was evident in the A- and B-waves of the compound action potentials of all seven

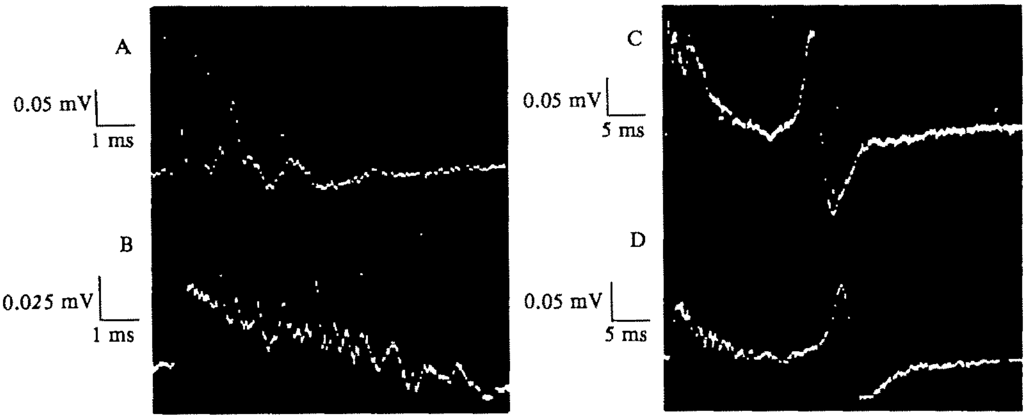

Fig. 2. Greater splanchnic nerve compound nerve action potentials. a, A-B-wave recorded from a control nerve showing three major deflections (β, $\gamma\delta$ and B). b, A-B wave from a nerve from a guinea pig with EAN showing marked temporal dispersion. c, biphasic C-wave recorded from a control nerve. d, biphasic C-wave recorded from a nerve from a guinea pig with EAN; the configuration is similar to the control but the amplitude is reduced.

splanchnic nerves from the guinea pigs with EAN (fig. 2B). In one nerve, no A- or B-wave could be recorded at the electrode most distant from the stimulating electrode while a small potential could be recorded from the electrode nearest the stimulus.

The C-waves of the splanchnic nerves from both the control and affected guinea pigs were biphasic (fig. 2C and D) and in some there were additional smaller peaks suggesting that there might be subpopulations of fibres grouped according to their conduction velocities. There was no obvious difference in the configuration of the C potentials of the two groups. In the case referred to above in which the A-B potential could not be recorded distally, the C potential could be recorded along the entire length of the nerve.

The values for conduction velocity and amplitude of the A-waves and the duration of the combined A- and B-waves of splanchnic nerves of control and affected guinea pigs are summarized in Table 1. There was significant slowing of conduction (42 per cent of control mean), reduction in amplitude and increased duration of the A-wave of the compound action potential in animals with EAN. The values for conduction velocity and amplitude of the C-wave are also summarized in Table 1. Although there was no significant difference in the conduction velocity of the C-wave, the amplitude was significantly reduced in animals with EAN. The mean impedance between the recording electrodes for the 6 control splanchnic nerves and for the 7 from affected animals was 52 kΩ (SD, 12) and 47 kΩ (SD, 10), respectively. The difference is not significant.

Histological Studies

Light microscopy. Peripheral nerves. In none of the sciatic nerves or spinal roots obtained from the control guinea pigs were there any features of demyelination or cellular infiltrates while in 9 of 16 (56 per cent) of those from affected animals foci of demyelination were seen, 5 of which were perivascular. Mononuclear cells were seen in these lesions but they were not very numerous. Demyelination was present in the lumbar nerve roots of 6 (38 per cent) of the 16 animals. In 12 animals (75 per cent) there was evidence of demyelination in the spinal roots and/or the sciatic nerve.

Autonomic nerves. No abnormalities were found in any of the control vagus or splanchnic nerves while in 4 (25 per cent) vagus nerves and in 9 (56 per cent) splanchnic nerves from 16 animals with EAN there was evidence of demyelination (fig. 3). Myelin debris was seen near demyelinated fibres in the vicinity of which was observed a small number of mononuclear cells. In two of the splanchnic nerves, almost all myelinated fibres were affected.

The total myelinated fibre density in three control vagus nerves was 57.7, 41.6 and 37.0 × $10^3/\text{mm}^2$ and in three vagus nerves from guinea pigs with EAN was 36.2, 28.7 and 22.1 × $10^3/\text{mm}^2$. In four control splanchnic nerves the total myelinated fibre density was 80.6, 70.7, 61.2 and 55.3 × $10^3/\text{mm}^2$ and in four splanchnic nerves from guinea pigs with EAN was 49.2, 38.0, 12.2 and 0.72 × $10^3/\text{mm}^2$. The myelinated fibre diameter distribution in these nerves is shown in figs. 4 and 5.

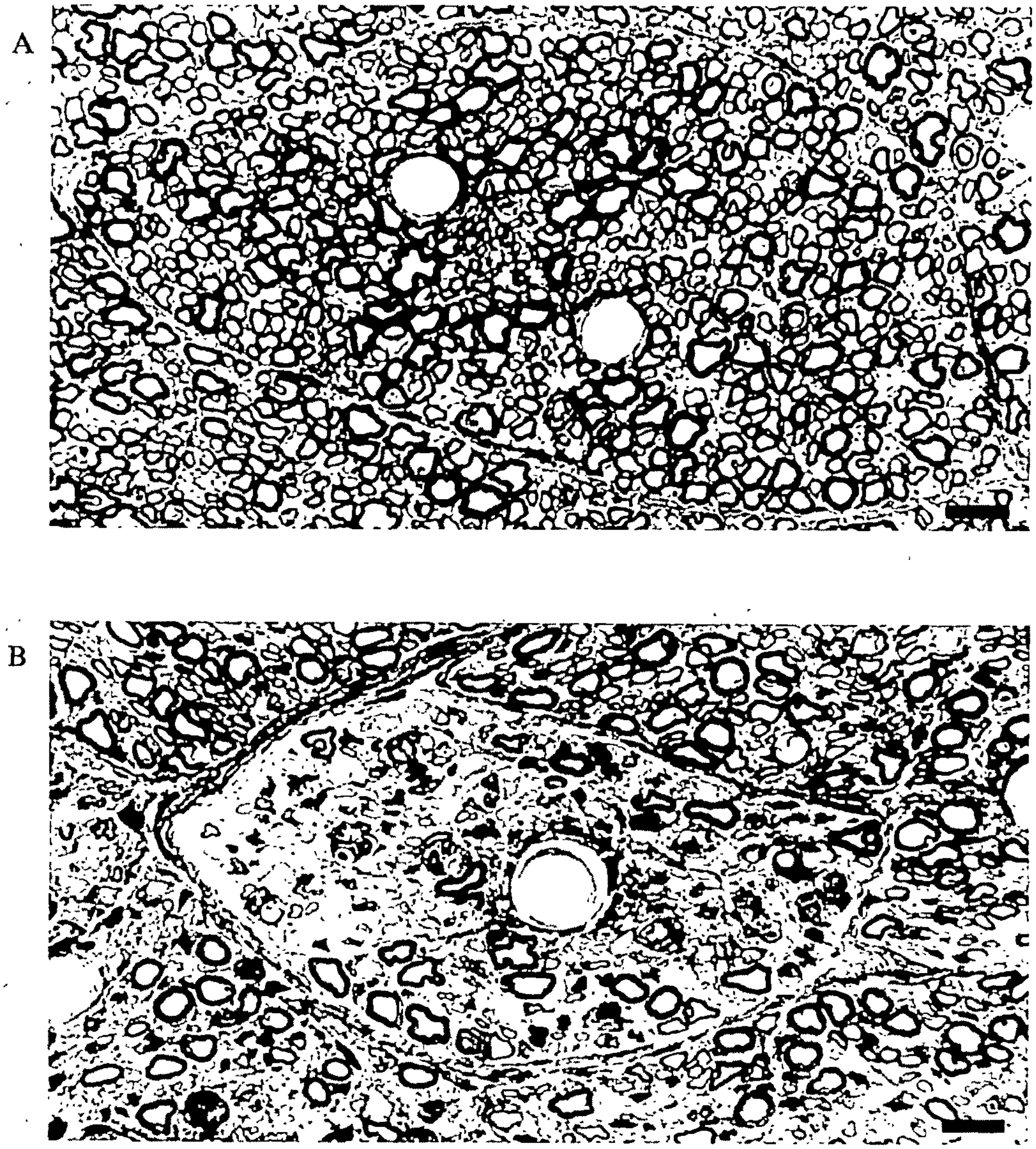

FIG. 3. Transverse sections of guinea pig right cervical vagus nerves. A, from a healthy guinea pig. B, from a guinea pig with EAN showing loss of many myelinated fibres in the centre fascicle (toluidine blue; scale 10 μm).

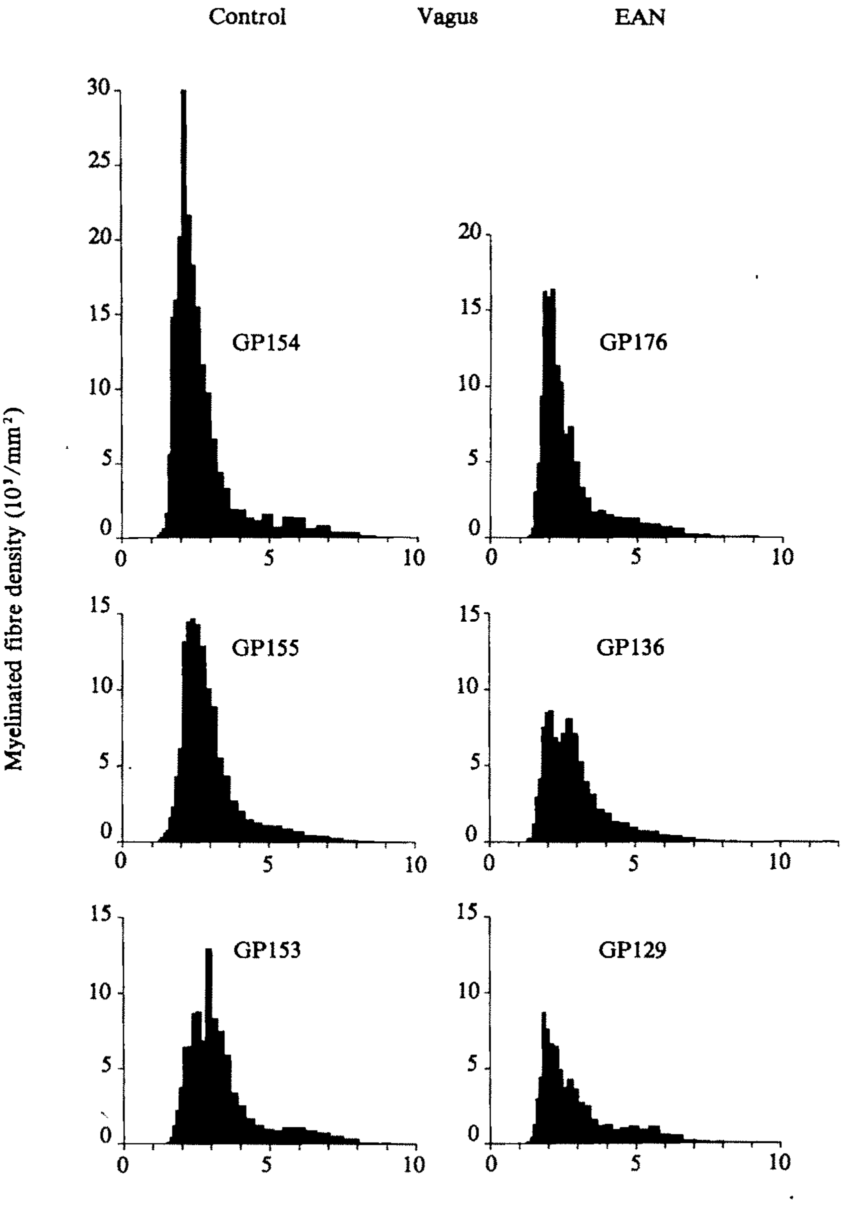

FIG. 4. Fibre diameter distribution of myelinated fibres of three right cervical vagus nerves from healthy guinea pigs and of three nerves from guinea pigs with EAN.

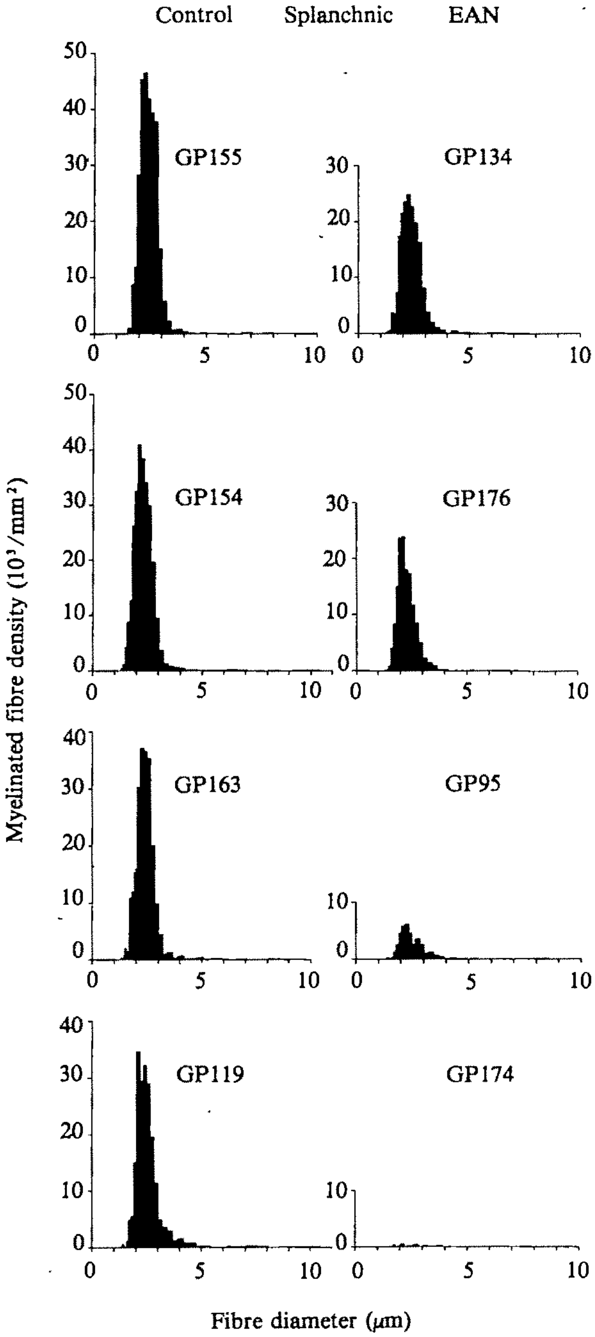

FIG. 5. Fibre diameter distribution of myelinated fibres of four left greater splanchnic nerves from healthy guinea pigs and of four nerves from guinea pigs with EAN.

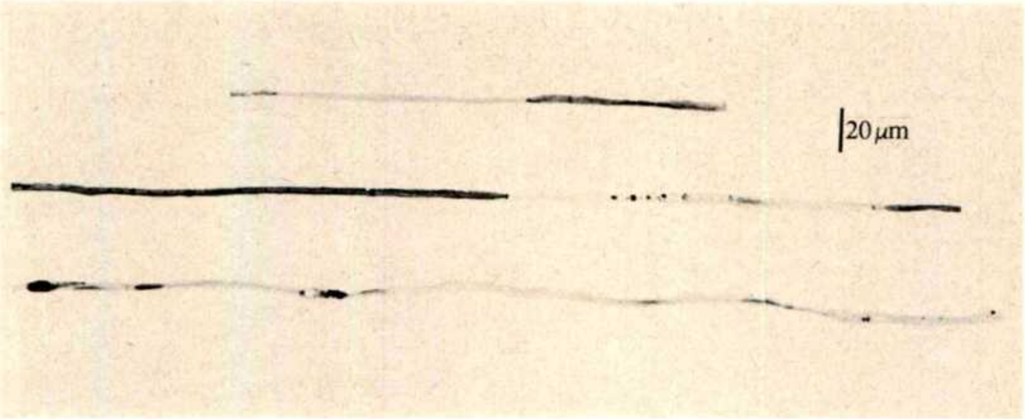

FIG. 6. Portions of three single fibres showing segmental demyelination teased from the cervical vagus nerve of a guinea pig with EAN (osmic acid, 1 per cent).

Changes consistent with either segmental demyelination or axonal degeneration were observed in 13 and 18 per cent of fibres teased from control vagus and splanchnic nerves, respectively. In the vagus and splanchnic nerves from animals with EAN, segmental demyelination was seen in 42 per cent of teased fibres while axonal degeneration was seen in approximately 30 per cent (Table 2; fig. 6).

TABLE 2. THE PERCENTAGES OF ABNORMALITIES IN TEASED FIBRES OF CONTROL AND AFFECTED VAGUS AND SPLANCHNIC NERVES

	Vagus		*Splanchnic*	
Fibre class[1]	*Controls*	*EAN*	*Controls*	*EAN*
A	81	22	82	26
B	6	3	0	0
C	0	2	6	2
D	10	40	7	40
E	1	31	5	32
F	0	0	0	0
G	0	1	0	0
H	2	1	0	0
Total	100	100	100	100

[1] Dyck (1975).

A = normal fibres. B = excessive irregularity as the only abnormality. C = paranodal demyelination. D = segmental demyelination with or without remyelination. E = linear rows of myelin ovoids or balls. E = fibres whose proximal portions consist of internodes of normal length (with or without demyelination) and distal to this the presence of linear ovoids or balls or a minimum of three short internodes. G = well myelinated fibres with focal enlargement forming sausages. H = normal appearance but with myelin ovoids on two or more contiguous internodes.

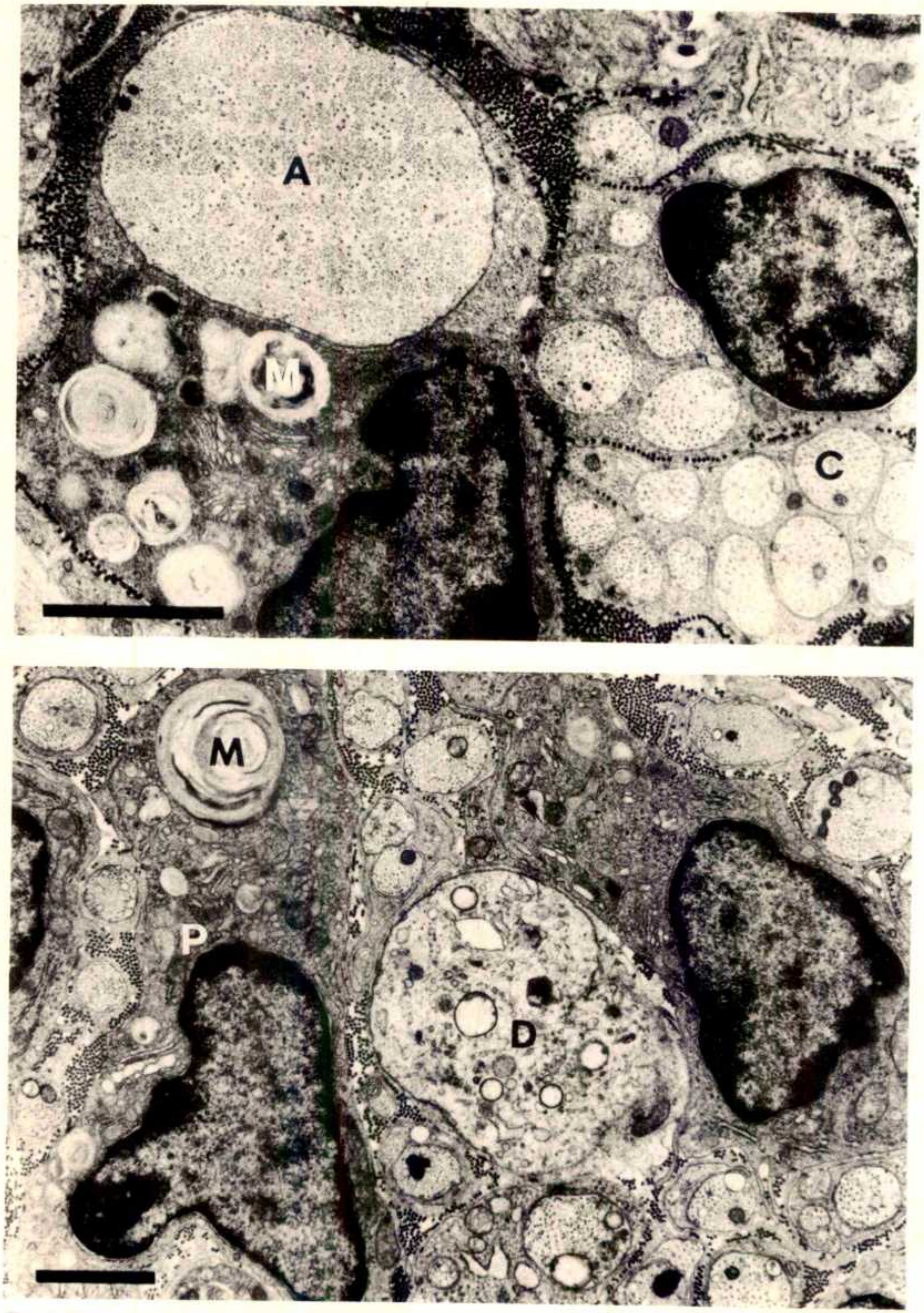

FIG. 7. Electron micrographs of the left greater splanchnic nerve from a guinea pig with EAN. A = demyelinated axon. C = unmyelinated fibres. D = degenerating axon. M = myelin debris. P = phagocytic cell (scale 5 μm).

Electron microscopy. In the vagus and splanchnic nerves from guinea pigs with EAN many of the larger nerve fibres were completely demyelinated and whorls of myelin debris were often present in the cytoplasm of adjacent phagocytic cells (fig. 7). Many of the demyelinated axons appeared to be normal although in some there were increased numbers of lysosomes, mitochondria, vesicles and dense bodies, which findings suggest axonal degeneration (fig. 7). In the splanchnic nerves axonal changes were found in some of the unmyelinated fibres (fig. 8) but no abnormalities were seen in any of the supporting cells of these unmyelinated fibre bundles.

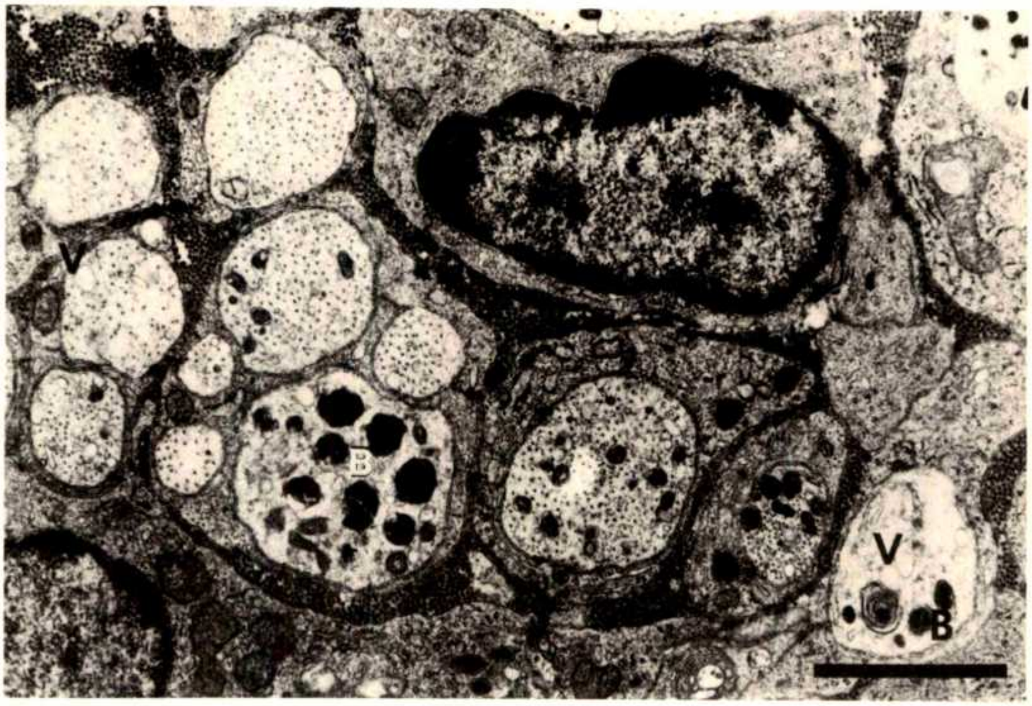

FIG. 8. Electron micrograph of the left greater splanchnic nerve from a guinea pig with EAN showing axonal degeneration in unmyelinated fibres. B = electron dense bodies. V = vesicles (scale 5 μm).

DISCUSSION

Pathological changes in the autonomic nervous system have only rarely been noted previously in EAN. Waksman and Adams (1955) described lesions involving the origin of the white rami in the rabbit; they found no lesions in the sympathetic ganglia of mice (Waksman and Adams, 1956). Pupillary dilatation in conjunction with weakness of external ocular muscles was described in monkeys with EAN by Wiśniewski, Brostoff, Carter and Eylar (1974) suggesting that parasympathetic fibres in the oculomotor nerves had been involved. In hyperacute EAN in baboons and Rhesus monkeys, lesions were observed in autonomic nerves while autonomic ganglia were relatively free of pathological changes (Behan, Feldman, Hunt and Behan, 1971).

Becker, Livett and Appenzeller (1978) briefly described changes in sympathetic chains of rabbits with EAN. They found heavy infiltrations of mononuclear cells but no destruction of either myelinated or unmyelinated fibres. Appenzeller, Arnason and Adams (1965) stated that sympathetic chains of nine rabbits injected with extracts of human sciatic nerve and Freund's adjuvant were normal. However, in animals injected with extracts of human sympathetic chain and Freund's adjuvant, some sympathetic ganglia and sciatic nerves contained mild perivascular infiltrates of lymphocytes and mononuclear cells. These authors concluded that the pathological changes observed did not account for involvement of the efferent sympathetic cholinergic fibres which were functioning abnormally.

Since intraperitoneal pertussis vaccine had been used previously to increase the incidence and severity of experimental allergic encephalomyelitis (Lee and Olitsky, 1955; Levine and Wenk, 1961) it was used as an additional adjuvant to increase the yield of affected guinea pigs in the present investigation. In a preliminary study of 80 guinea pigs injected with a mixture of peripheral nerve and Freund's adjuvant, 25 animals (31 per cent) developed very mild signs of weakness only while the remainder were unaffected (Tuck, 1980); when pertussis vaccine was used 70 per cent were affected, most of which had moderate or severe paralysis. There is no reason to suspect that the guinea pigs in the present study had the rapidly fatal hyperacute form of EAN induced in primates by Behan *et al.* (1971) when using pertussis vaccine as the clinical signs and the electrophysiological and histopathological changes in the peripheral nerves were identical to those in EAN reported by other workers (Waksman and Adams, 1956; Cragg and Thomas, 1964; Hall, 1967*a*, *b*).

The action potential recorded from the small muscles of the foot on stimulating the sciatic nerves was dispersed in the majority of clinically affected animals; similar findings have been reported by other workers (Cragg and Thomas, 1964; Hall, 1967*b*; Kraft, 1971). The mean maximal motor conduction velocity in affected guinea pigs was 84 per cent of the control mean. This reduction in conduction velocity is relatively mild but is consistent with the findings of others (Hall, 1967*b*; Lehmann, Lehmann and Tackmann, 1971). Kraft (1975) reported that the maximal motor conduction velocity was less than 30 m/s in 5 of 18 guinea pigs with EAN. In the present experiments conduction velocity was less than 30 m/s in only 2 of the affected animals. However, conduction velocity was measured between two and five weeks after injection with antigen, while Kraft (1975) found that the greatest slowing of conduction occurred at six weeks.

The configuration of the A-waves of the compound action potentials recorded from the cervical vagus nerves of the control guinea pigs in the present study resembles that of turtles and cats (Heinbecker, 1930; Bishop and Heinbecker, 1930; Li, Matthews and Bak, 1977). The conduction velocity in the guinea pig vagus nerve is slower than that in the cat, presumably because the diameter of the largest fibres in the nerve are 11 μm and 16 μm, respectively, in the two species (Post and McLeod, 1977). The C-waves of the cervical vagus nerve compound action potential were biphasic with the positive deflection often as large as the initial negative deflection; such biphasic C potentials with similar velocities as those in the present study have been recorded previously (Heinbecker, 1930; Bishop, 1934; Grundfest and Gasser, 1938; Gasser, 1950).

The mean maximal conduction velocity of the fourteen cervical vagus nerves from affected guinea pigs was reduced to 84 per cent of the control mean, which was the same as the reduction in motor conduction velocity in the peripheral nerves but was not as pronounced as sometimes occurs when segmental demyelination is present (Kaeser and Lambert, 1962; Fullerton and Barnes, 1966; Gilliatt, 1966; Bradley, 1970; Hopkins and Gilliatt, 1971; McLeod, Prineas and Walsh, 1973). However, relatively mild slowing of conduction is commonly found in the peripheral nerves of animals with EAN (Hall, 1967*b*; Lehmann *et al.*, 1971) and in patients with AIP (McLeod, Walsh, Prineas and Pollard, 1976) and is a reflection of the patchy distribution of the demyelinating lesions throughout the nerves (Hall, 1967*a*, *b*). Thus the relatively mild reduction in maximal conduction velocity of the vagus nerves of the guinea pigs with EAN is consistent with the same pathological process characterized by patchy demyelination which is known to affect the peripheral nerves. The appearance of the compound action potential and its increased duration indicated that temporal dispersion had occurred and the reduced time integral at distal recording sites indicated conduction block in some fibres. These findings are characteristic of segmental demyelination (McDonald, 1963; Cragg and Thomas, 1964; Hall, 1967*b*; Lehmann *et al.*, 1971; Denny-Brown and Brenner, 1944; Danta, Fowler and Gilliatt, 1971; Fullerton, 1966; Rasminsky and Sears, 1972). The mean amplitude and the maximal conduction velocity of the C potentials of the vagus nerves of guinea pigs with EAN were not significantly different from the controls, which is to be expected as the myelinated rather than unmyelinated fibres are primarily affected in this condition.

The compound nerve action potentials recorded from the greater splanchnic nerves of healthy guinea pigs consisted of $A\beta$, $A\gamma\delta$, B- and C-waves. The velocities of the A-waves were slightly less than those found in the splanchnic nerve of the cat (Amassian, 1951; McLeod, 1958; Widén, 1955; Post and McLeod, 1977), presumably because in the latter the largest fibres are 14 μm in diameter (McLeod, 1958; Post and McLeod, 1977) compared with 10 μm found in the guinea pig splanchnic nerve in the present study. The C potential of the compound action potential of the control guinea pig greater splanchnic nerve was, like that of the vagus, biphasic and resembled in configuration and conduction velocity those recorded from the sympathetic trunk and splanchnic nerve of the cat (Heinbecker, 1930; Grundfest and Gasser, 1938; McLeod, 1958; Li *et al.*, 1977).

The reduction in the mean maximal conduction velocity of the A-wave was more marked in the splanchnic nerves from affected guinea pigs than it was in the vagus nerves. The mean maximal conduction velocity was only 42 per cent of the control mean and in four nerves the velocities were 13 m/s or less. This finding, together with the temporal dispersion and increased duration of the compound action potentials suggested that demyelination was the major pathological change in the splanchnic nerve. The action potentials were too small and dispersed to permit measurement of their time integrals. Hence in all but one case, it is impossible to be certain whether there was block of conduction in some fibres as well as slowing of conduction.

An unexpected finding in the present study was that the mean amplitude of the C potentials of the splanchnic nerves from animals with EAN was significantly less than the control mean although there was no significant difference between the maximal conduction velocities of the two groups. The difference in the mean amplitudes is unlikely to have been due to the effect which interelectrode impedance has on the amplitude of a compound action potential (Hopkins and Lambert, 1972) since it did not differ significantly in the two groups. No other electrophysiological studies have been performed on C fibre conduction in EAN or other experimental demyelinating peripheral neuropathies although the amplitude of the C-wave of the compound action potential of the sural nerve of a patient with relapsing polyneuropathy was found to be normal by Lambert and Dyck (1975). Allt, Evans and Evans (1971) observed occasional Schwann cells associated with unmyelinated fibres being invaded by mononuclear cells in the peripheral nerves and spinal roots in EAN. If the supporting cells of C fibres are indeed damaged in EAN as is suggested by their observation, it is possible that conduction might also be affected adversely. It is also possible that unmyelinated fibres and their supporting cells might be damaged if they were 'innocent bystanders' in the vicinity of the immune process which is causing demyelination, as has been proposed to explain axonal degeneration in myelinated fibres in EAN by King, Thomas and Pollard (1977) and Madrid and Wiśniewski (1977). In the present study degenerating C fibres were observed with the electron microscope in the splanchnic nerve. Miyakawa, Muramaya, Sumiyoshi, Deshimaru, Kumana, Miyakawa and Tatetsu (1971) observed degeneration of unmyelinated fibres and their supporting cells in a sural nerve biopsied from a patient with AIP. It is possible therefore that the observed abnormality in C fibre conduction in the splanchnic nerves of guinea pigs with EAN might reflect direct or indirect damage to unmyelinated fibres. Becker *et al.* (1978) found no direct evidence of damage to unmyelinated fibres in the sympathetic chains of guinea pigs with EAN but their morphometric studies suggested that sprouting of unmyelinated fibres had occurred, providing indirect evidence that damage to C fibres had taken place.

The pathological lesions in the peripheral nerves of the affected guinea pigs resembled those in guinea pigs with EAN described by other workers (Waksman and Adams, 1956; Cragg and Thomas, 1964; Hall, 1967*a*) and the changes in the vagus nerves were identical to those observed in the sciatic nerves. The relatively few nerves in which pathological lesions were seen at only one site of section reflects their known patchy distribution. The appearance of the lesions in the splanchnic nerves from affected guinea pigs resembled those seen in the peripheral nerves but they appeared to be much more frequent and severe than those in the vagus nerves. In two nerves, almost all the fibres had been demyelinated.

The majority of individual teased fibres from vagus and splanchnic nerves of affected guinea pigs showed some type of pathological change. Although 42 per cent of fibres had features of segmental demyelination (types C and D), about 30 per cent appeared to be undergoing axonal degeneration (type E) which was an unexpected finding in a condition in which the predominant abnormality in the peripheral nerves is known to be segmental demyelination. However, axonal degeneration does occur in the peripheral nerves in EAN (King *et al.*, 1977) and according to Madrid and Wiśniewski (1977), small myelinated fibres are more likely to be so affected than large fibres. The majority of myelinated fibres in the guinea pig vagus and splanchnic nerves are of very small diameter.

The electron micrographs of the vagus and splanchnic nerves of guinea pigs with EAN support the conclusions that were drawn from the light microscope and teased fibre studies. Many myelinated fibres appeared to be normal while others were completely demyelinated with normal axons. However, some axons contained dense bodies and increased numbers of mitochondria and had lost their neurofilaments and microtubules indicating axonal damage (Schröder, 1975). These observations are contrary to those of Ballin and Thomas (1969), Lampert (1969), Schröder and Krücke (1970) and Allt (1975), who observed that axonal changes were infrequent in the peripheral nerves in EAN. Madrid and Wiśniewski (1977), however, observed that axonal degeneration was found more frequently in the peripheral nerves of the guinea pig with EAN than in the rabbit or baboon and that it tended to occur in the smallest myelinated fibres. The large numbers of small myelinated fibres in the guinea pig autonomic nerves and the high proportion of fibres undergoing axonal degeneration is consistent with their observation.

No abnormal unmyelinated fibres were seen in the vagus nerves from affected animals, but in the splanchnic nerves some were undergoing axonal degeneration although the majority appeared to be healthy. Quantitative studies were not performed on the unmyelinated fibres in these experiments so that it is not possible to be certain whether sufficient numbers were damaged to account for the reduction in the amplitude of the C components of the compound nerve action potentials observed in the splanchnic nerves of affected animals.

The clinical, histopathological and electrophysiological features of AIP and EAN are very similar (Waksman, 1959; Arnason, Asbury, Aström and Adams, 1968; Behan, Lamarche, Behan, Feldman and Kies, 1969; Arnason, 1971; Armstrong, 1972). Abnormalities resembling those found in peripheral nerves have been found in the vagus nerves of patients who have died with AIP by Bradford, Bashford and Wilson (1918-19), Roseman and Aring (1941) and Asbury, Arnason and Adams (1969). The splanchnic nerves have not been studied in AIP although changes in the sympathetic ganglia and sympathetic chains have been described by Sabin and Aring (1941), Parker and Adams (1947), Haymaker and Kernohan (1949), Matsuyama and Haymaker (1967) and Asbury *et al.* (1969). Clinical studies from patients with AIP suggest that the vagus and/or the splanchnic nerves may be affected in some patients with AIP (Barraclough and Sharpey-Schafer, 1963; Birchfield and Shaw, 1964; Lichtenfeld, 1971; Tuck and McLeod, 1978). Assuming that the distribution of lesions in the autonomic nervous system of humans with AIP is comparable to that in animals with EAN, it is likely that the splanchnic and vagus nerves would be affected in a proportion of patients with AIP.

SUMMARY

Electrophysiological and histological studies have been performed on the vagus and splanchnic nerves of guinea pigs with experimental allergic neuritis. Slowing of conduction and dispersion of the compound action potential were consistent with the pathological changes of demyelination. In teased single fibre preparations, axonal degeneration was found more frequently than was expected and in the splanchnic nerves, the unmyelinated fibres appeared to have been indirectly involved. These findings in experimental allergic neuritis are relevant to the pathogenesis of autonomic dysfunction in the Landry-Guillain-Barré syndrome.

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(*Received July 3, 1980*)

Brain (1981), **104**, 209–214

NOTICES OF RECENT PUBLICATIONS

Progress in Clinical Neurophysiology. Edited by J. E. Desmedt. Basel: Karger.

Volume 6. **Cognitive Components in Cerebral Event-Related Potentials and Selective Attention.** 1979. Pp. 322. Price DM 141.00.

Volume 7. **Clinical Uses of Cerebral, Brainstem and Spinal Somatosensory Evoked Potentials.** 1980. Pp. 354. Price DM 165.00.

From their titles one might expect the first of these volumes to be aimed mainly at physiological psychologists and the second at clinical neurologists; but in fact Volume 6 ends with four chapters on clinical applications, and the first half of Volume 7 is devoted almost entirely to analysis of cortical and far-field somatosensory evoked potential (SEP) components in normals, so there is something for everyone in both.

The study of evoked (or more generally, 'event-related') potentials (EPs) has not always captured the enthusiasm of neurophysiologists. To those accustomed to the labour and frustrations of winning data from single units there is something almost indecent about the relative ease with which anyone with an averaging computer can turn out reams of publishable results—results, moreover, whose relation to underlying neuronal activity is still obscure, as Desmedt, Goff and others here emphasize. It must be admitted also that many methodological snags in EP recording have been slow to be recognized, with the result that much of the early work is now suspect or valueless. What books such as these demonstrate, however, is that the kinds of data now reliably obtainable by EP methods can resolve questions to which answers at the level of single-unit activity would be too 'fine-grained' to serve the purpose. The two methods, both scientifically and clinically, are usefully complementary.

This point is brought out particularly by the main section on Conscious Perception and Cerebral Event-Related Potentials (Volume 6). S. A. Hillyard and T. W. Picton, in a wide-ranging and critical review, illustrate the growing value of EPs as almost our only window on to the physiological correlates of normal cognitive information processing. They stress the importance of topographic analysis—well implemented, for example, by W. Ritter and colleagues (Volume 6) and by T. A. Duff (Volume 7)—as a means of distinguishing components of a response complex which have different sources. Neglect of this precaution by one or two of the other symposiasts considerably reduces the value of their papers.

A point not brought out clearly is that where two EP components (thus identified) have opposite polarity, both latency and height of the peaks in the combined waveform will generally be affected by any changes in relative component amplitudes, even where component latencies remain unaltered. It is thus desirable to maintain a distinction between 'peaks' and 'components', especially (as in many clinical applications) when looking for changes in *component* latency. Too many of the present contributors unfortunately follow the custom of identifying components with peaks, and using peak latencies as their labels.

Although clues to the depth of an EP source can often be gained from scalp distributions, special interest attaches to direct investigations like those of W. R. Goff and colleagues (Volume 7) using multielectrode probes implanted (for other purposes) in the brains of three epileptic patients. Quite consistent depth profiles were obtained for somatic, auditory and visual EPs with peak latencies above 70 ms. They confirm that the familiar vertex potentials can be recorded bilaterally and diffusely in the depths of the brain. Relative to linked ears, these show inversion of polarity with depth for somatic, but not for auditory, stimulation. Such results highlight the uncertainties that beset efforts to compute deep source locations from scalp distributions. Further work on depth profiles, both in patients and in suitable animals, could fill a major gap in present knowledge.

Another major gap is in our understanding of the electrogenesis of EPs. It is clear from the relevant chapters here that we still have only the haziest notions as to what physiological changes these potentials reflect. For certain clinical or psychophysical purposes it may not matter whether a given peak originates in dendritic depolarization, somatic hyperpolarization, glial activity, or other candidate processes; but before EP recording can realize its full capacity as a bridge between single-unit physiology and cognitive processes, questions of this kind will have to be resolved. Comparative studies, exemplified here by W. C. Wiederholt's chapter on Early Components of Somatosensory Evoked Potential in Man, Cat and Rat (Volume 7), reveal intriguing differences between EPs to analogous stimuli in different species; but these give no reason to doubt that key experiments in animals could dispel some of the most frustrating of our present uncertainties.

A brief review cannot do justice to the richness of these well-documented surveys, each volume of which offers a combined list of over 500 references. Several chapters focus on aspects of the contingent negative variation (CNV) that precedes the resolution of cognitive uncertainty, and its relations on the one hand to the motor readiness potential or Bereitschaftspotential (BP), and on the other to the briefer P300 wave-complex associated with unexpected stimuli. In each case justice is done to the controversial state of the art. An attempt by S. J. Purves and colleagues to correlate visual EPs with stimulus shape and 'information content', however, fails to reckon with the fact that the shape of at least the first 200 ms of the scalp-recorded EP can vary enormously with the retinal location of the stimulus (because of the folding of the cortical projection). Without careful controls for this accidental factor it is impossible to draw general conclusions at the level of information-content analysis.

A stimulating chapter by D. H. Ingvar analyses the activation patterns revealed by cerebral blood flow measurements during diverse cognitive phases. Maturation of EPs and changes with ageing are covered in two wide-ranging surveys by D. Kurtzberg *et al.* and E. Courchesne. Specifically clinical sections explore the relevance of EP data in various psychiatric cases as well as in neurological diagnosis, where their usefulness appears to be well recognized. As far as a non-clinician can judge, these volumes form a worthy addition to a reference series of established value.

D. M. MACKAY

Handbook of Psychopharmacology. Edited by L. L. Iversen, S. D. Iversen and S. H. Snyder. Volume 9. **Chemical Pathways in the Brain.** 1978. Pp. 410. New York and London: Plenum Press. Price $29.50.

This book is extremely valuable to any research worker in the field of transmitters in the brain for two reasons: first, it summarizes the extensive and scattered literature on the anatomy of central pathways with known transmitters; this is done in great detail and includes many figures and photomicrographs from the original papers as well as new contributions from the authors of the chapters. Secondly, it gives details of most of the methods used, with critical comments and useful comparisons between the available methods. This is particularly helpful in the chapters on immunochemistry (A. C. Cuello) and on acetylcholine (P. R. Lewis and C. C. D. Shute), since the original papers usually limit themselves to describing the technique employed in the particular paper.

The main transmitters discussed are the catecholamines, 5-hydroxytryptamine, γ-aminobutyric acid (GABA) and substance P, with short mention of glycine, glutamate, releasing factors, somatostatins, enkephalins and vasoactive intestinal peptide. An introductory chapter (R. Y. Moore) deals with surgical and chemical lesion techniques and includes a most welcome list of stereotaxic atlases. L. L. Iversen describes the autoradiographic techniques which have proved useful in localizing transmitters and brings details of the distribution of GABA in neurons and glia and of the antagonists capable of distinguishing between these two locations. Cuello illustrates the immunofluorescence techniques which show up the localization of catecholamines and GABA by their synthesizing enzymes, and a number of peptides by antibodies to the transmitter itself. A detailed account of neurons containing catecholamines (Lindvall and Björklund) is very largely based on the authors' own findings and photomicrographs. The chapter on 5-hydroxytryptamine (Azmitia) makes use of improved techniques (radio-autography after the injection of labelled proline) to show the widespread, almost ubiquitous occurrence of serotonergic fibres and terminals, which had not been evident when only fluorescence microscopy was available. The fact that most brain cells appear to be under the influence of 5-HT-containing cells localized in the raphe nuclei has suggested that the serotonergic neurons may not be responsible for a specific behaviour but modulate the expression of such behaviour. It is regrettable that the anatomical information summarized in this chapter only covers the dorsal and median raphe nuclei, whereas the pathways of the caudal and rostral nuclei are not equally well defined. The basis of the widespread distribution of serontonergic neurons seems to be the tendency, during prenatal development, of the outgrowing fibres to follow existing pathways of more mature non-serotonergic fibres.

In the last two chapters Shute and Lewis describe the cholinergic system and Fonnum and Storm-Mathisen GABA-ergic neurons. Although cholinergic neurons were the first to be described in the brain, their role in physiology and pathology is still rather ill-defined, and their precise anatomy sometimes in doubt because of certain discrepancies between the occurrence of cholinesterase and cholineacetyltransferase. This is partly due to cholinesterase being required at the surface of cholinoceptive cells as well as of cholinergic neurons. In contrast, the role of GABA appears to be unambiguous inhibition, either post- or presynaptic. The occurrence of GABA in glial cells does not pose any problems of localizing GABA-containing neurons, since the decarboxylase which forms GABA can be detected by radioimmunoassay and is not present in glia.

The excellent habit of listing all abbreviations used in a paper on its first or second page is adopted by some of the authors; and perhaps it is permissible to make a plea for universal adoption of this method.

MARTHE VOGT

Willis's Oxford Lectures. Edited and introduced by Kenneth Dewhurst. 1980. Pp. 181. Oxford: Sandford Publications. Price £9.00.

Dr Dewhurst recently published a fascinating work on Schiller, reviewed in *Brain* by Professor Alfred Meyer. His new book on Willis opens with a short but highly documented biographical chapter. Although much is known about Willis' professional and family life, not to speak of his investments in property, no clear picture of the man's personality emerges. Dewhurst found him an industrious physician, whose treatments, though occasionally nauseating, were simple and safe. A devout person, who treated poor patients without charge, Willis was generous in his charity. His family life was clouded by the deaths of his first wife and several young children. In contrast with his scientific work, he had secret remedies of iron and sulphur prepared by his private apothecary and gained financially from the public demand for these nostra. The genius displayed in his contributions to medical science sprang from a tireless boldness of thought.

The lectures contained in this book are more concise and less controversial than his published writings, and they cover his most creative years. They have come down to us, mostly in Latin, from John Locke's notebooks and Richard Lower's manuscript and occupy some two-thirds of the book. The topics covered are almost all neurological or psychiatric; Willis tended to regard mental illness as a manifestation of brain disorder. The blending of Galenical notions and humoral pathology with his important anatomical observations and clinico-pathological studies is a reflection of contemporary medical thought. At that time the division between scientific and pragmatic or empirical clinicians was deep; Locke appears to have deserted Willis for Sydenham.

Doctor Dewhurst's task was worthwhile, and it has been well accomplished. He has provided an interesting picture of medicine after the Restoration of the Monarchy, including the ways to preferment in those times. More importantly, he has given his readers the opportunity to study the teachings of a neurological founder, teachings recorded by a most distinguished student. His book is recommended to all who are interested in the beginnings of scientific neurology.

R. A. HENSON

Folic Acid in Neurology, Psychiatry and Internal Medicine. Edited by M. I. Botez and E. H. Reynolds. 1979. Pp. 534. New York: Raven Press. Price $62.56.

It is timely that a comprehensive treatise should appear on this difficult and complex subject. The roles and importance of folic acid in neurology, psychiatry and internal medicine have been matters of controversy for many years.

Whilst numerous clinical reports have appeared describing syndromes of the central and peripheral nervous systems associated with folate deficiency (many of the earlier ones depending merely on low serum folate levels) inevitably the issue has been clouded by associated alterations of serum vitamin B_{12} levels and the possibility of other deficiency states being present, especially when there is co-existing intestinal disorder, and nowhere have the difficulties been greater than in those patients on anticonvulsant therapy.

It is clear that much fundamental research concerning the basic role of folate and its precursor in brain is being carried out in a number of laboratories, and the scene is now set for the systematic investigation of folate biochemistry—especially in relation to structure-activity relationships with neurotransmitter and receptor systems. It is surprising, however, that many of the clinical problems remain unresolved, and readers of this book will not find answers to many of the old questions. However, the problems have now been more clearly defined and many of the relevant questions more clearly posed, especially those relating to folate and B_{12} interactions.

Folic Acid in Neurology, Psychiatry and Internal Medicine comprises the proceedings of an international symposium held in Montreal in 1979. As such it covers a wide range of topics and many of the authors are acknowledged to be leading authorities in their respective fields. In general, the chapters are short and most have a useful summary at the end. This is particularly important as this is a reference volume, there being a mixture of review articles and original papers. It is useful though to have much of the new relevant scientific data covered in one volume.

I find the opening chapter, which poses many of the problems in historical perspective, particularly useful and with advantage this might have been somewhat longer and more detailed. It has to be admitted, however, that some material in the book must be regarded as controversial and a number of ideas, particularly those concerned with a specific folate myelopathy, would probably be accepted with reserve by many neurologists, at least in the current state of knowledge.

Neurologists will probably find the section on clinical neurology, epilepsy and vitamin B_{12}/folate interactions most useful. Important topics covered in these sections include the convulsant properties of folate, the role of folic acid in patients with peripheral neuropathy who are on anticonvulsant therapy and other neurological disorders ascribed to folate deficiency. Elsewhere in the book the important question of folate absorption and the effect of anticonvulsants on this is covered.

The sections on biochemistry and neurochemistry are useful research material for the specialist laboratory worker. Topics covered in these sections include methodology and the importance of folate determination in biological material, the role of folate in the developing brain (also dealt with in a further chapter on the section on experimental neurology) and the important question of interaction between folate and monoamines with particular reference to seizure threshold.

Two chapters are devoted to folate and the CSF, and these are mainly concerned with the close correlation between serum and CSF concentrations both in health and disease and the mechanisms of folate transport across the blood/brain barrier.

In the penultimate section of the book, there is a particularly useful interpretative chapter which is both balanced and appropriately critical, and which deals with an overview on the difficult problem of folate deficiency and it relevance to a range of neuropsychiatric disorders.

It is clear, therefore, from this treatise that in the present state of knowledge many problems remain unsolved. The convulsant properties of folic acid, however, now appear to be established on a firm scientific basis, though the relative importance of the various mechanisms involved remains to be elucidated.

The book is well-produced and the diagrams are clear. It is an irritation, however, that different sections are not clearly indicated in the text so that reference has to be made back constantly to the contents. The index is adequate and the bibliography (which is mainly up to 1978) is a useful classified guide to the diverse literature on this subject.

The book can be recommended as a reference volume which is likely to be of interest to most clinical neurologists, and also to those neurochemists interested in becoming involved in an area of biochemistry which is of emerging importance in relation to common clinical neurological problems.

P. T. LASCELLES

Advances in Neurology, Volume 27. **Antiepileptic Drugs: Mechanisms of Action.** Edited by G. H. Glaser, J. K. Penry, and D. M. Woodbury. 1980. Pp. 750. New York: Raven Press. Price $93.84.

This volume represents an extensive compilation of topics on antiepileptic drugs that has long been desired. It is a comprehensive review of anticonvulsant drug actions which encompasses both basic and clinical studies. Early chapters are devoted to the review of basic mechanisms of neurobiology which are essential to understanding the underlying causes of abnormal electrical activity in the brain. The latter portion of the book deals with both pharmacokinetics and pharmacodynamics of the various classes of anticonvulsant drugs.

The chapters on neurobiology of epilepsy deal with many possible ætiologies for the initiation and propagation of seizure activity. Basic principles, for example, synaptic transmission, are well presented and add to the over-all scope of the book. The section on structure-activity relationships of antiepileptic drugs is presented in such a way as to make a rather difficult subject readily understandable. In addition, there is an excellent chapter on convulsant drugs.

The sections on pharmacokinetics and pharmacodynamics are very well organized and presented, especially regarding phenytoin and phenobarbital. Other anticonvulsant drugs, including valproate, are also discussed, although not to the extent of the more classic compounds. While it is recognized that not as much is known about these newer antiepileptic drugs, one might wish that a more detailed review of them could have been included.

Overall, this book answers an interesting challenge of combining multiple disciplines to produce a volume which will serve not only as an excellent introductory textbook, but will educate the beginning and advanced investigator in the field as well. It is an informative and well written addition to the anticonvulsant literature.

MICHAEL R. VASKO

Advances in Experimental Medicine and Biology. Volume 125. **Structure and Function of Gangliosides.** Edited by Lars Svennerholm, Paul Mandel, Henri Dreyfus and Paul-Francis Urban. 1980. Pp. 571. New York and London: Plenum Press. Price $49.50.

Since the discovery of gangliosides in nervous tissue and the elucidation of the structure of the storage lipid found in Tay-Sachs' disease, there has been a truly remarkable increase in our knowledge of the chemistry and function of this class of glycolipid. Gangliosides form a complex family of lipids distinguished by their ceramide-linked carbohydrate residue which include up to five sialic acid

(N-acetyl neuraminic acid) moieties. Gangliosides have a prime role on the outer membrane surface as recognition sites. Thus, the hydrophobic (e.g. sphingosine) part of the molecule is inserted in the bimolecular lipid layer and the carbohydrate residues project in a pattern from the surface. At the external surface of the synapse gangliosides such as the monosialo ganglioside GMI may be involved in calcium exchange and neurotransmission. It has even been suggested that neuronal gangliosides are involved as receptors for biogenic amines. It is not surprising, therefore, that it appears that permanent behavioural changes can be induced by injection of young animals with antibodies to GMI ganglioside. These effects are also no doubt related to the importance of gangliosides in synaptic interaction and in morphological differentiation of cells grown in tissue culture. In this respect, glycolipid changes associated with oncogenic transformation have been extensively studied.

Gangliosides have recently attracted considerable attention as receptors for various bacterial toxins, viruses, interferon and glycoprotein hormones (e.g. thyrotropin). GMI has been identified as the receptor molecule for cholera toxin. This has led to the use of the ganglioside for large-scale affinity chromatographic isolation of cholera toxin for the preparation of effective vaccine therapy.

It is evident that papers on the topic of structure and function of gangliosides are likely to be of general biological interest. This is true of many of the fifty or so articles from the proceedings of a symposium held in 1979, now published in *Advances in Experimental Medicine and Biology*. In the first part there are papers on new chemical methods for analysis and isolation and this is followed by accounts of the distribution and metabolism of gangliosides. There is an important section on immunological methods for identification, one on sialidoses (e.g. the mucolipidoses) and on functions.

This comprehensive volume is well produced, and in general the separate chapters knit together in an interesting and readable way.

A. N. DAVISON

FORTHCOMING EVENTS

Migraine Symposium at The 12th World Congress of Neurology on September 22, 1981. Abstracts (less than 100 words) not later than May 1, 1981 to:

Dr F. Clifford Rose
Princess Margaret Migraine Clinic
Charing Cross Hospital
London W6 8RF.

The Third World Congress of the International Association for the Study of Pain will be held in Edinburgh, Scotland, between September 4–11, 1981.

Details and application forms may be obtained from:

Pain Congress Secretariat
The University of Edinburgh
Centre for Industrial Consultancy & Liaison
16 George Square
Edinburgh EH8 9LN, UK.

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FUNDAMENTALS OF VISCERAL INNERVATION *by* **Budh Dev Bhagat** *and* **Paul A. Young,** *both of St. Louis Univ., St. Louis, Missouri, and* **Donald E. Biggerstaff,** *Southern Illinois Univ., Springfield, Illinois. '77, 216 pp., 91 il., 18 tables, cloth-$31.25, paper-$21.50*

New! **THE FACIAL PALSIES: Their Physiopathology and Therapeutic Approaches** *by* **Joseph Moldaver** *and* **John Conley,** *both of Columbia Univ. College of Physicians and Surgeons, New York, New York. (5 Contributors)* This monograph offers reliable, detailed coverage of the etiology, physiopathology, and surgical and nonsurgical treatment of the various facial palsies. Peripheral nerve pathology, reflexes and clinical signs related to the facial nerve, Bell's Palsy, and the surgical approach to the facial nerve are among the chapter topics which will be of special interest to neurologists. *'80, 272 pp. (6 3/4 x 9 3/4), 155 il., $35.75*

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AMYOTROPHIC LATERAL SCLEROSIS AND ITS ASSOCIATION WITH DEMENTIA, PARKINSONISM AND OTHER NEUROLOGICAL DISORDERS: A REVIEW

by ARTHUR J. HUDSON

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INTRODUCTION

AMYOTROPHIC lateral sclerosis (ALS) is widely regarded as a disease that is confined to the voluntary motor system with progressive degeneration of the corticospinal tracts and alpha motor neurons leading to extreme muscular weakness and wasting (Munsat and Bradley, 1979). Amyotrophic lateral sclerosis, when defined in this way, encompasses progressive muscular atrophy and progressive bulbar palsy but excludes other neurological and organ system involvement. An objection to this concept is that, pathologically, there are often features of more extensive change in the nervous system in ALS than the degeneration of the upper and lower motor neurons and, clinically, there are a number of reports of dementia, parkinsonism and sensory changes occurring in association with ALS (Smith, 1960; Bonduelle, Bouygues, Escourolle and Lormeau, 1968; Brownell, Oppenheimer and Hughes, 1970; Brait, Fahn and Schwarz, 1973; Mitsuyama and Takamiya, 1979). If ALS is a more complex disorder than is generally recognized then the clinical and pathological features that are a part of the degenerative process as it extends beyond the corticospinal tracts and lower motor neurons have yet to be clearly identified.

While the term 'motor neuron disease' often has been preferred to ALS when reference is also being made to progressive muscular atrophy and progressive bulbar palsy, such a large number of diseases of the motor neuron qualify for this title that ALS seems to offer the advantage of specificity. But this advantage is uncertain since a number of apparently different conditions have now been identified as ALS because of identical features of lower and upper motor neuron degeneration. For this reason the well-known forms of sporadic and familial ALS, as they occur in the adult and clinically affect only the upper and lower motor neurons, are referred to as 'classical' ALS. Other types of ALS are distinguished by their occurrence in the very young or the presence of additional features. These include sporadic and familial

ALS in the juvenile, ALS with dementia and parkinsonism, post-encephalitic ALS, Guamanian and other Western Pacific forms of ALS and the ALS form of Creutzfeldt-Jakob disease. It is noteworthy that ALS in the juvenile and ALS with dementia and/or parkinsonism, while generally not accepted as part of the classical syndrome, nevertheless have no clear identity. ALS with dementia, for example, has been variously regarded as a new entity (Mitsuyama and Takamiya, 1979), a form of Creutzfeldt-Jakob disease (van Rossum, 1968) and as a variant of classical ALS (Masters, Harris, Gajdusek, Gibbs, Bernoulli and Asher, 1979).

In the present study an extensive review has been made of dementia, parkinsonism and other neurological features that have been described in the literature as accompanying ALS. The objective has been to determine, if possible, whether they are variants of the classical syndrome or separate entities.

CLASSICAL ALS

Classical ALS can be described as a disease of progressive wasting and weakness of the bulbar and spinal skeletal musculature with variable signs of fasciculation and pyramidal impairment due to degeneration of the lower and upper motor neurons. These basic features are common to all of the different forms of ALS. While classical ALS is usually considered to be a sporadic disease it, nevertheless, includes both sporadic and familial cases since they are clinically undifferentiable except for familial history. It is estimated that only 5 to 10 per cent of cases of ALS have a family history (Mulder, 1957; Bonduelle, Bouygues, Lormeau and Keller, 1970; Rosen, 1978). The incidence could be greater since ALS is a disease of late onset and it is probable that in some cases other family members who would eventually develop ALS die before that time from other, more common, causes. There are many reports of familial ALS in the literature and these will be discussed separately from the sporadic disease.

1. *Sporadic ALS*

(*i*) *Clinical findings.* In 1973 Bobowick and Brody in an epidemiological review of motor neuron disease discussed the various population surveys in Europe and the United States to that time. Since then there have been four more surveys in Europe and two more in the United States that support the earlier data. From the ten most complete epidemiological studies (Gudmundsson, 1968; Lorez, 1969; Cendrowski, Wender and Owsianowski, 1970; Matsumoto, Worth, Kurland and Okazaki, 1972; Kahana, Alter and Feldman, 1976; Jokelainen, 1977*a*; Rosati *et al.*, 1977; Zack, Levitt and Schoenberg, 1977; Bracco, Antuono and Amaducci, 1979; Juergens, Kurland, Okazaki and Mulder, 1980) it can be estimated by using mean values of the available data that in Europe and the United States (including Hawaii) classical ALS has, approximately, a male to female ratio of 2:1, an incidence of 1 per 100000 population, mean age of onset of 56 years and mean age at death of 59 years. In the series in which both the age of onset and death are recorded the mean duration of

ALS is about 2.5 years. Epidemiological or other surveys very seldom make special reference to unusual features of ALS such as dementia and parkinsonism but such cases are sometimes included under the heading of classical ALS. Brownell *et al.* (1970) included a case of ALS with dementia and another with parkinsonism in their series of 36 'typical' cases. Jokelainen (1977*b*) observed psychic alteration in 39 of a total 255 ALS cases (15 per cent) including 5 cases with dementia (2 per cent). Dementia can easily escape recognition in bulbar cases of ALS or be misinterpreted as an emotional reaction of the patient to the illness. Similarly, extrapyramidal signs can be obscured by extensive weakness and wasting of muscle (Masini, Canal and Guazzi, 1965).

(*ii*) *Pathological findings*. Brownell *et al.* (1970), in a detailed examination of the nervous system in 45 necropsies of cases of ALS, divided the study into two parts. The first part, consisting of 36 sporadic cases of ALS, were considered to be 'typical' (classical) and the remaining 9 were regarded as 'atypical'. Only the first group of 'typical' cases needs discussion although the 'atypical' group had many similarities.

Pathologically, all the 36 'typical' cases showed loss of lower motor neurons and there was pyramidal tract degeneration in 80 per cent (28 cases). Posterior column degeneration was described in less than 10 per cent (3 cases) of the series. Cerebral atrophy was present in one-third and in almost two-thirds of the subjects there was abnormal gliosis in one or more structures such as the cerebral cortex, thalamus, corpus striatum, globus pallidus, subthalamic nucleus and substantia nigra. Two patients showed status spongiosus of the cerebral cortex.

The findings of Brownell *et al.* are in agreement with those reported by Smith (1960) who observed degenerating myelinated fibres throughout the cortex, basal ganglia, substantia nigra and other regions in a study of 7 cases of classical ALS.

Lawyer and Netsky (1953) found gyral atrophy in the frontal region in 13 of 53 cases of ALS. All but 2 of their cases showed pyramidal tract degeneration whereas only one case showed degeneration of the posterior columns (fasciculus gracilis). Other authors also have found degenerative changes, not only in the motor cortex where they are often present, but in the frontal pre-motor and opercular regions (Friedman and Freedman, 1950). Degeneration of the spinothalamic pathway has been noted by Davison (1941).

2. *Familial ALS*

(*i*) *Clinical findings*. In 1955 Kurland and Mulder collected a total of 18 families with ALS that had been reported over the preceding one-hundred years and added 6 pedigrees of their own (124 cases). In 1959 Faveret also made an extensive review of the literature collecting 29 families (121 cases) of ALS of adult onset (*see also* Bonduelle, Bouygues and Faveret, 1959). In Table 1 are listed the families with ALS who have been described since the report of Kurland and Mulder to 1980. Included are those accounts which specified, as a minimum, the numbers of both the generations and cases with their sex who undoubtedly had ALS. This gave 61

TABLE 1. FAMILIAL AMYOTROPHIC LATERAL SCLEROSIS

Author	No. of families	No. of generations	No. of cases	M/F ratio	Mean age at onset	Mean age at death	Mean duration* (years)	Comment
I. Classical (Adult) ALS								
Hasaerts-van Geertruyden (1955)	1	2	2	1/1	60	—	—	Autopsy
Boudin and Barbizet (1956)	2	2	4	3/1	49	50	1	
		2	2	1/1	63	65	2	
Bonduelle and Bouygues (1957)	1	2	6	1/5	40	45	5	
Dierssen Gervas (1959)	1	3	6	6/0	—	70	—	
Engel, Kurland and Klatzo (1959)	1	4	11	4/7	—	39	1	Family A, autopsy: Family B reported by Hirano *et al.* (1967)
Faveret (1959)	2	1	2	2/0	35	—	6	
		1	2	0/2	48	—	—	
Green (1960)	1	4	7	4/3	—	—	—	
Magee (1960)	1	1	3	3/0	47	—	11	Autopsy
Lopez Aydillo (1960)	1	2	2	2/0	44	—	—	
Espinosa, Okihiro, Mulder and Sayre (1962)	1	2	8	2/6	39	—	14	
Serd and Kovarik (1963) (Family 1)	1	2	3	2/1	—	—	—	
Tsubaki, Kazinuma and Nakamura (1963)	1	2	4	3/1	—	36	—	Autopsy (*see* Kubo, Ikuta and Tsubaki, 1967)
Bourrat, Boulliat, Trillet and Vedrinne (1963)	1	2	3	1/2	44	—	3	
Roe (1964)	2	2	3	0/3	48	50	1.5	Multiple sclerosis in 2 other members in first family
		2	3	3/0	—	53	—	
Poser, Johnson and Bunch (1965)	1	4	5	1/4	47	48	1	
Boudouresques *et al.* (1966)	1	2	2	2/0	43.5	45	1.5	
Hirano *et al.* (1967)	1	2	4	2/2	49	51	1.5	Family B of Engel *et al.* (1959); autopsy
Houff, Calabrese and Taylor (1976)	1	2	4	0/4	—	—	22	
Avanzini, Lechi and Mancia (1968)	1	4	8	7/1	45	48.5	3	
Thomson and Alvarez (1968)	1	3	6	6/0	—	29	2	Family of Montonaro and Lopez with 2 new cases; autopsy
Alajouanine and Nick (1959)	1	1	3	2/1	59	—	7	
Moya, Miranda-Nieves and Perez Sotelo (1969)	1	2	4	2/2	30	32	1.5	Autopsy
Dumon *et al.* (1971)	1	1	2	2/0	44	—	—	Dizygotic twins (consanguinous parents)
Metcalf and Hirano (1971)	1	4	21	10/11	40	52	11.5	Sensory symptoms; autopsy

Arnould *et al.* (1972)	1	2	5	3/2	35	37	2	Autopsy
Takahashi *et al.* (1972)	1	3	5	2/3	—	47	2	Autopsy
Orthner, Becker and Müller (1973)	1	1	2	0/2	38	40	2	Consanguinous parents
Igisu *et al.* (1974)	1	6	11	6/5	42	—	1	Autopsy
Alter and Schaumann (1976*b*) (Family 2)	1	2	6	2/4	46	49	2.5	
Horton, Eldridge and Brody (1976)	13	2(5 families) 1(8 families)	34	18/16	51.4	—	3	
Swerts and van den Bergh (1976)	1	3	9	7/2	37	41	3	
Estrin (1977)	1	1	2	2/0	56	—	—	Dizygotic twins
Gimenez-Roldan and Esteban (1978)	1	3	5	2/3	50	53	7	
II. ALS-Dementia-parkinsonism (Adult)								
Robertson (1953)	1	2	4	2/2	—	67	—	ALS-dementia; autopsy
van Bogaert and Radermecker (1954)	1	2	3	3/0	32	—	6	ALS-parkinsonism; autopsy
Campanella and Bigi (1959)	1	1	5	5/0	31	48	20	ALS-dementia
Serd and Kovarik (1963) (Family 2)	1	2	6	3/3	—	—	—	ALS-dementia-extrapyramidal signs
Dazzi and Finizio (1969)	1	4	7	1/6	45.5	51.5	—	ALS-dementia
Yvonneau, Vital, Belly and Coquet (1971)	1	3	4	2/2	63	69	6	ALS-dementia, extrapyramidal signs; autopsy
Finlayson, Guberman and Martin (1973)	1	2	4	2/2	—	68	2.5	ALS-dementia; autopsy
Pinsky, Finlayson, Libman and Scott (1975)	1	2	3	2/1	54	58	4	ALS-dementia; autopsy
Alter and Schaumann (1976*b*) (Family 1)	1	2	6	6/0	50	52	1.5	ALS-dementia, extrapyramidal and sensory signs; autopsy
Hestnes and Mellgren (1980)	1	3	7	5/2	—	—	—	ALS-dementia
III. ALS in Childhood								
Refsum and Skillicorn (1954)	1	1	3	2/1	4	—	23	
Staal and Went (1968)	1	1	7	3/4	10	26	15	Associated dementia; consanguinous parents
Myllylä *et al.* (1979)	1	1	2	1/1	19	—	—	

* Average duration of ALS based on interval from onset to death or duration of survival if greater than one year per individual.

families (270 cases) and included 3 families with ALS of juvenile onset, 2 sets of twins with ALS in both of the pairs, and 10 pedigrees of ALS of adult onset with dementia and/or parkinsonism in one or more affected members.

If the 3 families with ALS beginning in childhood and the 10 families with dementia and/or parkinsonism are excluded, a comparison of the present review can be made with the earlier comprehensive reviews of Kurland and Mulder and Faveret. The data based on the remaining 48 families (210 cases) with ALS of adult onset shows a male to female ratio of 1.3:1 (Kurland and Mulder, 1.2:1 and Faveret, 1.1:1), a mean family age at onset of 47.3 years (Faveret, 46.8 years; Kurland and Mulder, age at death, 47.4 years) and a mean family duration of 4.1 years using data from 38 families based on the interval from onset to death or duration of survival of greater than one year per individual (Faveret, 2.7 years). From these data familial ALS appears to have a lesser male preponderance and a younger mean age of onset than sporadic ALS. In three-quarters of the families ALS occurred in 2 or more generations.

TABLE 2. DISTRIBUTION OF CASES OF AMYOTROPHIC LATERAL SCLEROSIS, DEMENTIA AND EXTRAPYRAMIDAL SIGNS IN FAMILIAL AMYOTROPHIC LATERAL SCLEROSIS*

Family of	*ALS only*	*Dementia only*	*Extra-pyramidal only*	*ALS-dementia*	*ALS-extrapyramidal*	*ALS-dementia-extrapyramidal*
Robertson (1953)	3			1**		
van Bogaert and Radermecker (1954)	2**		2**		1	
Campanella and Bigi (1959)	4			1		
Sercl and Kovarik (1963)	5					1
Dazzi and Finizio (1969)	6			3		
Yvonneau *et al.* (1971)	2			1		1**
Finlayson *et al.* (1973)	2	1		2**		
Pinsky *et al.* (1975)	2			1**		
Alter and Schaumann (1976*b*) (Family 1)	1			2**	1	2**
Hestnes and Mellgren (1980)	6			1		

* Extrapyramidal signs refer to rigidity and/or tremor and was sometimes described as parkinsonism.

** Pathological findings also reported.

Dementia was described in 9 families (15 per cent) and parkinsonism in one family with ALS. As shown in Table 2 usually only one or two cases of ALS-dementia occurred in a family. In 3 families some members with ALS had both dementia and extrapyramidal signs (*viz*, tremor and rigidity). Dementia occurred independently from ALS in only one case and it is probable, therefore, that ALS and dementia are closely related. Dementia preceded, accompanied or followed the onset of ALS but appeared, most often, to follow onset. The sex ratio, age of onset and duration of the ALS were similar in the families with ALS-dementia to those with classical ALS.

van Bogaert and Radermecker (1954) described a family in which one member had ALS and parkinsonism while 2 other family members had ALS and 2 had only parkinsonism. Other familial combinations of ALS and parkinsonism in association with dementia or cerebellar disorder have been reported. Alter and Schaumann (1976*a*) described a family in which one member had ALS while 3 of the patient's relatives who did not have ALS had a combination of parkinsonism and dementia. Biemond and Sinnege (1955) studied a family with cerebellar ataxia occurring in combination with ALS and parkinsonism.

There are two reports of ALS occurring in adult dizygotic twins—one pair from consanguinous parents—and both twins in each set had ALS (Dumon, Macken and de Barsy, 1971; Estrin, 1977). No other members of either family had ALS. In the only report of ALS occurring in a monozygotic twin only one of the twins had acquired the disease to the time of reporting two years after the death of the affected twin at the age of 68 years (Jokelainen, Palo and Lokki, 1978).

Sensory changes consisting of a glove and stocking hypæsthesia with complaints of numbness and tingling have been encountered in familial ALS by Metcalf and Hirano (1971) and Alter and Schaumann (1976*b*). Earlier workers, notably Wechsler, Brock and Weil, (1929) also reported a 'neuritic' type of sensory disturbance in sporadic cases of ALS. Reports of sensory findings in ALS have been challenged by Feller, Jones and Netsky, (1966).

(*ii*) *Pathological findings*. Twelve families with classical ALS have had a detailed pathological examination of the central nervous system. Two families, who could not be included in Table 1 because of insufficient clinical detail (Fleck and Zurrow, 1967; Farmer and Allen, 1969), were included in the pathological review. In addition, 3 families had ALS which, in one or more members, was accompanied by dementia and another family had ALS combined with dementia and extrapyramidal features. These 4 families will be discussed separately from the 12 classical families.

In the 12 families with classical ALS a detailed autopsy examination was usually done on only one member but in 3 families there was more than one autopsy (Hirano, Kurland and Sayre, 1967, Cases 1 and 2; Farmer and Allen, 1969; Igisu, Ohta, Yamashita and Kuroiwa, 1974; Table 3). The pathological findings in these families were generally similar although variations were found. In 10 of the families (80 per cent) at least one member showed degenerative change in the posterior column (70 per cent of autopsies). This is in contrast to the sporadic form of classical ALS in which posterior column degeneration occurs in less than 10 per cent of cases (Lawyer and Netsky, 1953; Brownell *et al.*, 1970). The degeneration in the posterior column was present in either the middle root zone of the fasciculus cuneatus or the fasciculus gracilis, or both. In 6 of the 10 families with posterior column

TABLE 3. NEURONAL AND LONG TRACT DEGENERATION AND GLIOSIS IN FAMILIAL AMYOTROPHIC LATERAL SCLEROSIS

Author	*Anterior horn cells*	*Pyramidal tract*	*Posterior column*	*Clarke's column*	*Spino-cerebellar tract*	*Cerebral cortex*		*Special features**	*Other structures*
						Region	*Layers*	*S, T, SP, PB, GV*	
I. Classical Familial ALS									
Hasaerts-van Geertruyden (1955)	+	+	+	−	−				
Engel *et al.* (1959)	+	+	+	+	+	Diffuse			Posterior horn cells
Magee (1960)	+	−	+						
Fleck and Zurrow (1967)	+	+	−	−	−	Frontal, temporal	3, 5		
Hirano *et al.* (1967)									
Case 1	+	+	+	+	+				Cerebellum; inferior olives
Case 2	+	+	+	+	+				
Case 4	+	+	+	+	+				
Case 5	+	+	−	−	−				
Kubo *et al.* (1967) (*see* Tsubaki *et al.*, 1963)	+	+	+	+	+				Posterior horn cells; spinothalamic pathway
Farmer and Allen (1969)									
Case 1	+	−	+	+	−				
Case 2	+	−	−	+	−				
Moya *et al.* (1969)	+	−	+	−	−	Frontal			Globus pallidus; substantia nigra; corpus Luysii, olive
Metcalf and Hirano (1971)	+	+	+	+	+				
Arnould *et al.* (1972)	+	−	−	−	−				Substantia nigra; olive
Takahashi *et al.* (1972)	+	+	+	−	−				
Igisu *et al.* (1974)									
Case 1	+	+	+	+	−				
Case 2	+	−	−	+	−				
Case 3	+	−	−	−	−				
*II. Familial ALS-Dementia***									
Robertson (1953)	+	+	−		−	Frontal, temporal		SP	
Finlayson *et al.* (1973)									
Case 1	+	+	−		−	Frontal, temporal	2, 3	S	Cases 1 and 2 similar: amygdala; neurofibrillary tangles in locus caeruleus and periaqueduct grey
Case 2	+	+	−		−	Frontal, temporal	2, 3	S	
Pinsky *et al.* (1975)	+	+	−		−	Frontal, temporal	2, 3	S	
*III. Familial ALS-dementia-extrapyramidal Signs***									
Yvonneau *et al.* (1971)	+	+	+		+	Diffuse			Caudate nucleus; putamen

* S = status spongiosus; T = neurofibrillary tangles; SP = senile plaques; PB = Pick's bodies; GV = granulovacuolar degeneration.

** Cases shown had ALS-dementia and/or parkinsonism. van Bogaert and Radermecker (1954) and Alter and Schaumann (1967*b*) cases not included because of insufficient pathological detail on ALS-dementia and/or parkinsonism patients.

degeneration there was also evidence of degeneration of Clarke's column and in 4 of these there was spinocerebellar tract degeneration. In contrast to the latter findings, Brownell *et al.* (1970) noted the absence of specific spinocerebellar tract degeneration or involvement of Clarke's column in all 36 of their cases of sporadic ALS. Pyramidal tract degenerative change was present in two-thirds of the cases of familial ALS.

Neuronal degeneration in the cerebral cortex was reported in 3 subjects from separate families with classical ALS. In 5 families neuronal degenerative change and gliosis in at least one member was found in other structures such as the globus pallidus, corpus Luysii, substantia nigra, cerebellum, inferior olives and the posterior horns of the spinal cord. In 3 families hyaline and argentophilic inclusion bodies with a deep-staining central core were found in the anterior horn cells (Hirano *et al.*, 1967; Metcalf and Hirano, 1971; Takahashi, Nakamura and Okada, 1972).

In the 3 families with autopsies in which ALS had been combined with dementia, all the autopsies showed upper motor neuron loss but no posterior column or spinocerebellar degeneration (Table 3). Cerebral cortical atrophy was present in every case of ALS-dementia and this was mainly frontotemporal. Neuronal degeneration, status spongiosis in the upper layers and gliosis were the main pathological features in the cortex.

In the single autopsy of a case with ALS, dementia and extrapyramidal disorder, diffuse degeneration of the cerebral cortex, caudate nucleus and putamen was found.

ALS WITH DEMENTIA AND/OR PARKINSONISM (SPORADIC)

(*i*) *Clinical findings.* A total of 42 cases of sporadic ALS with dementia and/or parkinsonism was reviewed. Only cases with clinical features of motor neuron degeneration which were typical of classical ALS and sufficiently detailed information for tabulation were included in the study. Two cases with a survival period of twenty-five years (Masini *et al.*, 1965; Ishii, Nishimaru, Okumura and Kikuchi, 1976) and a patient with cerebellar signs (Brait *et al.*, 1973), although otherwise similar to the above cases, were excluded. Twenty-six subjects had ALS with dementia, 8 had ALS with parkinsonism and the remaining 8 showed ALS with a combination of dementia and parkinsonism. The dementia in these cases had, in the main, the same clinical features as characterize Alzheimer's or Pick's disease. In Table 4 the age of onset and duration of ALS, dementia and parkinsonism in the 3 groups are shown.

The male to female ratio for the entire group of ALS with dementia and/or parkinsonism was 2.2 : 1, similar to classical sporadic ALS. The mean age of onset of ALS in the entire series was 53.3 years and did not differ significantly when determined as ALS with dementia or ALS with parkinsonism. The mean age of onset of dementia was 52.1 and of parkinsonism 53.9 years for the entire series.

TABLE 4. AMYOTROPHIC LATERAL SCLEROSIS-DEMENTIA-PARKINSONISM (NON-FAMILIAL)

		Age at onset			Duration				
Author	*Sex*	*ALS (yrs)*	*Dementia (yrs)*	*Parkinsonism (yrs)*	*ALS (yrs)*	*Dementia (yrs)*	*Parkinsonism (yrs)*	*Course*	*Comment*
I. ALS-parkinsonism									
Cordier (1951)	M	30	—	39	9	—	< 1	Progressive	
Patrikios (1951)	M	59	—	59	1	—	1	Progressive	Numbness preceded onset of ALS by six months
Greenfield and Matthews (1954)	M	56	—	31	1	—	26	Died	No history of encephalitis but authors regarded case as post-encephalitic; autopsy
Bonduelle, Bouygues, Delahousse and Faveret (1959)	M	70	—	70	0.75	—	0.75	Progressive	
Legrand, Linquette, Delahousse and Gérard (1959)	M	70	—	66	0.5	—	4	Progressive	
Brait *et al.* (1973)									
Case 1	F	68	—	64	2	—	6	Died	
Case 2	M	60	—	59	4	—	5	Progressive	Also had recurrent lipomyosarcoma
Case 3	M	53	—	50	3	—	6	Progressive	
II. ALS-dementia									
Meyer (1929)	M	55	55	—	0.75	0.75	—	Died	Autopsy
Ziegler (1930)									
Case 1	F	50	47	—	1.5	4	—	Died	
Case 2	M	50	50	—	1	1	—	Died	
Case 3	F	58	59	—	4	2.5	—	Died	
Wechsler and Davison (1932)	M	36.5	36	—	1.5	2	—	Died	Autopsy
Teichmann (1935)	M	43	43	—	1.25	1.25	—	Died	Autopsy
Friedlander and Kesert (1948)	M	47	49	—	3.5	1	—	Died	
Léchelle, Buge and Leroy (1954)	M	45	41	—	0.5	4	—	Died	Sister died of dementia
Michaux, Samson, Harl and Gruner (1955)									
Case 1	F	58	58	—	2	2	—	Died	Aphasia also; autopsy
Case 2	M	56	58	—	2	< 0.5	—	Died	Aphasia possibly two years
Delay, Brion, Escourolle and Marty (1959)									
Case 1	F	55	56	—	2	1	—	Died	Autopsy
Case 2	M	58	60	—	3	1	—	Died	Autopsy

van Reeth *et al.* (1960)	M	52	48	—	2	6	—	Died	Autopsy
Myrianthopoulos and Smith (1962)	M	66	70	—	5	1	—	Died	Autopsy
von Matt (1964)	F	57	57	—	0.5	0.5	—	Died	Autopsy
Yuasa (1964)	M	47	47	—	1.25	1.25	—	Died	
Harada, Kozaki and Harayama (1966)	M	61	60	—	2	3	—	Died	Extrapyramidal tremor; autopsy
De Morsier (1967)	M	57	52	—	2	7	—	Died	Autopsy
Shirabe, Inoue, Izumi and Kikuchi (1970)	F	38	38	—	1	1.25	—	Died	Autopsy
Yuasa (1970)	F	53	53	—	2	2	—	Died	Autopsy
Mitsuyama and Takamatsu (1971)	F	59	58	—	1	2	1	Died	Autopsy
Kaiya (1972)	M	45	45	—	1.3	1.75	—	Died	Autopsy
Kaiya and Mehraein (1974)									
Case 1	M	43	43	—	2	2	—	Died	Autopsy
Mitsuyama and Takamiya (1979)	F	58	58	—	4	4	—	Died	Autopsy
Personal Cases									
Case 1	F	56	56	—	1.5	1.5	—	Died	Autopsy
Case 2	M	58	59	—	1	0.5	—	Died	Autopsy
III. ALS-dementia-parkinsonism									
Wechsler and Davison (1932)									
Case 2	M	30	32	< 32	3	1	U*	Died	Autopsy
Case 3	F	49	< 50	< 50	1	U*	U*	Died	Autopsy
Caidas, Marcutu and Vuia (1966)	M	60	60	61	1	1	< 1	Died	Forme fruste, parkinsonism; autopsy
Boudouresques *et al.* (1967)	M	51	53	54	3	2	1	Died	Autopsy
Tsujiyama, Shigeta, Kudo and Takayama (1967)	M	42	40	42	1	3	1	Died	Autopsy
Bonduelle *et al.* (1968)									
Case 1	M	65	67	66	2	0.3	0.8	Died	Autopsy
Case 2	F	59	57	60	1.5	3	0.5	Died	Autopsy
Kaiya and Mehraein (1974)									
Case 2	M	57	58	60	4	3	1	Died	Autopsy

* U = unknown.

Thus, the age of onset, and therefore the duration of illness, was almost the same for ALS, dementia and parkinsonism which suggests that they are part of the same process. The mean duration of ALS was 2.1 years.

(*ii*) *Pathological findings*. Twenty-seven of the 42 cases of ALS with dementia and/or parkinsonism which were reviewed had pathological studies of brain and spinal cord (Table 5).

Lower motor neuron degeneration was observed in all 27 cases. Three-quarters of the subjects showed pyramidal tract degeneration whereas posterior column degeneration was present in only 2. Thus, the incidence of long tract degeneration was similar to the classical sporadic disease with less than 10 per cent of cases showing posterior column degeneration. Apart from these features the cases of ALS with either dementia or parkinsonism, or both, showed some differences.

In 18 of the 27 autopsy cases, ALS had been accompanied only by dementia. Gross inspection of the brain in the majority of these cases showed atrophy that varied from negligible to marked and was mainly in the frontal and/or temporal lobes. There were degenerative changes and disappearance of neurons with gliosis in the cerebral cortex in all 18 cases and in half of the subjects these changes were predominant in layers 2 and 3 in the frontal and temporal regions. Often a spongey appearance of the cortex was present in these layers. In 3 subjects degenerative changes were found, mainly, in the 3rd, 5th and 6th layers. In three-quarters of the patients there was alteration and loss of neurons and/or gliosis in one or more of the corpus striatum, globus pallidus, thalamus, corpus Luysii, substantia nigra, dentate nucleus and other subcortical regions of the nervous system. Clinical evidence of impairment in these regions was apparently not observed. Alzheimer's neurofibrillary tangles, granulovacuolar degeneration or Pick's argentophilic inclusions were not found. Senile plaques were found in one case.

In 8 of the 27 autopsies, ALS, dementia and parkinsonism had been combined. Cerebral cortical degenerative changes were present, mainly, in the frontal or frontotemporal regions in all cases. In 6 cases degeneration and loss of neurons, gliosis and spongioform degeneration were found in layers 1, 2 and 3 of the cortex while in the remaining 2 subjects, neuronal loss and gliosis were predominant in cortical layers 3, 5 and 6. Degeneration of the substantia nigra or globus pallidus was reported in all but one case and neuronal loss or gliosis was found in other neuronal structures, such as the corpus striatum, thalamus and corpus Luysii, in all subjects.

The remaining case had parkinsonism and ALS without dementia and showed marked neuronal loss and gliosis in the substantia nigra and globus pallidus with neurofibrillary tangles in the former structure. The authors (Greenfield and Matthews, 1954) viewed this case as post-encephalitic ALS-parkinsonism (*see below*) although there was no history of encephalitis.

ALS IN CHILDREN

ALS has been described in children but its relationship with classical ALS is uncertain. It is rare and may be sporadic or familial. The difficulty in identification was noted by Faveret (1959) who collected 11 reports of alleged sporadic ALS and 27 accounts of familial ALS occurring in children. However, when the cases with aberrant features, such as ocular palsy and chorea, were excluded there was only one sporadic case and 5 families with the features of classical ALS.

1. *Sporadic ALS in Children*

(*i*) *Clinical findings.* Because of preselection on the basis of an appearance that resembles classical ALS, cases of sporadic juvenile ALS are usually indistinguishable from the classical disorder if the age of onset is disregarded. There are 4 cases that fit the classical clinical criteria with sufficient pathological detail for analysis. The cases described by Wohlfart and Swank (1941), Berry, Chambers, Duckett and Terrero, (1969), Nishigaki, Takahashi and Matsuoka, (1971) and Nelson and Prensky (1972) include 3 males and one female with a mean age of onset of 14.5 years (range 12 to 16 years) and a mean duration of illness of sixteen months (range twelve to eighteen months).

(*ii*) *Pathological findings.* Lower motor neuron and pyramidal tract degeneration, but no other long tract changes, were present in all the above cases. Neuronal degeneration and/or intracytoplasmic basophilic inclusions were observed in the cortex, subcortical and brain-stem nuclei and spinal motor neurons in the cases of Berry *et al.* (1969) and Nelson and Prensky (1972). The same neuronal inclusions were noted by Wohlfart and Swank (1941) in their case but no details of the changes in brain were given.

2. *Familial ALS in the Child*

(*i*) *Clinical findings.* Further to the account of Faveret (1959), 3 families with a motor neuron disorder that resembles classical ALS have been described (Table 1). Apart from the clinical appearance, the juvenile familial syndrome differs in a number of important aspects from the familial adult condition. In the juvenile disorder transmission appears to be autosomal recessive in contrast to a pattern of dominant inheritance in most adult families and survival averages fifteen or more years. Also, aberrant features such as dementia, which prompted Faveret to exclude many families with juvenile ALS, are frequent. In one of the families shown in Table 1 all but one of 7 affected siblings had an associated dementia (Staal and Went, 1968; Staal and Bots, 1969). The male to female incidence in the 3 families was similar (1 : 1) and the mean age of onset was 11 years.

TABLE 5. NEURONAL AND LONG TRACT DEGENERATION AND GLIOSIS IN AMYOTROPHIC LATERAL SCLEROSIS-DEMENTIA AND/OR PARKINSONISM

Author	*Anterior horn cells*	*Pyramidal tract*	*Posterior column*	*Clarke's column*	*Spinocerebellar tract*	*Cerebral cortex*		*Special features**	*Other structures*
						Region	*Layers*	*S, T, SP, PB, GV*	
I. ALS-parkinsonism									
Greenfield and Matthews (1954)	+	–	–		–	–	–	T	Globus pallidus, substantia nigra
II. ALS-dementia									
Meyer (1929)	+	+	–			Temporal			Caudate nucleus, putamen, globus pallidus, thalamus, hypothalamus, corpus Luysii
Wechsler and Davison (1932)									
Case 1	+	+	–		+	Frontal	5, 6		Basal ganglia and thalamus (slight), paraventricular nuclei
Teichmann (1935)	+	+	–	+	+	Frontal	3, 5, 6		Basal ganglia, periaqueduct grey, purkinje cells, dentate nucleus, posterior horn
Michaux *et al.* (1955)	+	+	–	–		Frontal, temporal, parietal	2, 3		Substantia nigra, thalamus, corpus Luysii
Delay *et al.* (1959)									
Case 1	+	+				Frontal, temporal	1, 2 (3)	S	
Case 2	+	+				Frontal, temporal	2	S	Ammon's horn
van Reeth *et al.* (1960)	+	+	+			Frontal, temporal insula and cingulate gyrus	2, 3 (5)	Ballooning of cells	Caudate nucleus, putamen, globus pallidus, substantia nigra, (locus caeruleus)
Myrianthopoulos and Smith (1962)	+	+				Temporal	1, 2, 3	S	
von Matt (1964)	+	–	–			Diffuse			
Harada *et al.* (1966)	+	+	–			Frontal, temporal and insula			Globus pallidus, thalamus
De Morsier (1967)	+	+	–			Frontal, temporal		SP	Substantia nigra; olive

Shirabe *et al.* (1970)	+	+	–			Frontal, temporal	1, 2		Putamen, globus pallidus, substantia nigra, dentate nucleus
Yuasa (1970)	+	+				Frontal	1, 2	S	Basal ganglia; substantia nigra
Mitsuyama and Takamatsu (1971)	+	+				Frontal, temporal	2, 3	S	Torpedoes in cerebellum
Kaiya (1972)	+	+	–			Frontal	All layers		Globus pallidus, thalamus, corpus Luysii, substantia nigra, red nucleus
Kaiya and Mehraein (1974)									
Case 1	+	–	–	–	–	Frontal	3, 5		Corpus striatum, pallidum, thalamus, substantia nigra, olive, posterior horn cells
Personal Cases									
Case 1	+	–	–	–	–	Frontal	2, 3, 5	S	Hippocampus
Case 2	+	+	–	+	+	Frontal			Substantia nigra
III. ALS-dementia-parkinsonism									
Wechsler and Davison (1932)									
Case 2	+	+	–		–	Frontal	3, 5, 6		Globus pallidus, corpus Luysii
Case 3	+	+	–		+	Frontal, temporal	3, 5, 6		Globus pallidus, accessory olivary nuclei, locus caeruleus
Caidas *et al.* (1966)	+	–	–		–	Frontal	3	S	Globus pallidus, substantia nigra
Boudouresques *et al.* (1967)	+	+	+		+	Frontal, temporal	Upper layers (notably 3)	S	Caudate nucleus, putamen, globus pallidus, thalamus, substantia nigra, corpus Luysii, red nucleus, locus caeruleus
Tsujiyama *et al.* (1967)	+					Frontal, temporal	1, 2, 3	S	Dentate nucleus
Bonduelle *et al.* (1968)									
Case 1	+	+				Frontal	2, 3	S	Thalamus, substantia nigra
Case 2	+	+				Frontal	1, 2, 3	S (T, GV-Ammon's horn)	Caudate nucleus, thalamus, substantia nigra
Kaiya and Mehraein (1974)									
Case 2	+	–				Frontal	2, 3	S	Corpus striatum, globus pallidus, substantia nigra, thalamus, dentate nucleus, posterior horn cells

* S = status spongiosus; T = neurofibrillary tangles; SP = senile plaques; PB = Pick's bodies; GV = granulovacuolar degeneration.

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(*ii*) *Pathological findings.* Only one autopsy report was available and this was on a member of the family with ALS-dementia (Staal and Bots, 1969). There was severe loss of anterior horn cells and marked degeneration of both the pyramidal pathways and fasciculus gracilis with loss of fibres also in the spinocerebellar tracts. Clarke's columns were intact. The lesions in the brain were in the white matter with perivascular loss of substance throughout the hemispheres and the cerebellum and especially marked in the basal ganglia. There was also degeneration of the spinal ganglion cells. The cerebral and cerebellar cortex were normal. The pathological findings in this case indicate an entirely different entity from classical ALS.

POST-ENCEPHALITIC ALS

(*i*) *Clinical findings.* Following the epidemics of encephalitis lethargica which peaked in 1920 and again in 1924 there were two notable neurological sequelæ of which the most widely recognized was post-encephalitic parkinsonism. The other was post-encephalitic ALS which has been well described by French and German authors. Brait *et al.* (1973) have made a detailed clinical summary of the literature on post-encephalitic ALS with and without parkinsonism.

Post-encephalitic ALS was first recognized by Froment and Gennevois in 1921 and four years later, Froment (1925) reported on the death of the same patient. There are 25 case reports of post-encephalitic ALS which, for the most part, satisfy the clinical criteria of classical ALS with the exception of the presence of extrapyramidal features, characteristic of parkinsonism (ALS-parkinsonism), in two-thirds of the subjects (Table 6). The average age of onset of the encephalitis in these cases was 28 years. The male to female ratio was 1.5:1. The average interval from the acute encephalitis to the onset of ALS was ten years ranging up to thirty years. Thus, the mean age of onset of ALS was almost 40 years. The duration of ALS was 3.8 years when only those subjects who were deceased were included (11 cases). In all but 2 of the cases of ALS-parkinsonism in which the intervals from encephalitis to the onset of ALS and extrapyramidal signs were known, parkinsonism appeared before or at the same time as ALS. While intellectual impairment was a feature of encephalitis it was only occasionally mentioned in relation to post-encephalitic ALS.

(*ii*) *Pathological findings.* There are very few detailed reports of pathological changes in the nervous system in cases with progressive motor neuron degeneration following encephalitis lethargica. Two accounts of necropsies on subjects who had post-encephalitic ALS and parkinsonism have demonstrated extensive involvement of the nervous system (Hirano and Zimmerman, 1962; McMenemey, Barnard and Jellinek, 1967). The pathological findings of a case reported by Greenfield and Matthews (1954) are not included since it is uncertain that the patient ever had encephalitis lethargica (*see* Table 4). Nevertheless, it is of interest that neurofibrillary tangles were present in this case as in those described below.

Table 6. Post-Encephalitic Amyotrophic Lateral Sclerosis [ALS and ALS-parkinsonism]

Author	*Sex*	*Age at onset of encephalitis (yrs)*	*Interval to onset of ALS (yrs)*	*Duration of ALS (yrs)*	*Extrapyramidal signs*	*Course*	*Comment**
Froment and Gennevois (1921) and Froment (1925)	F	31	0.5	3	None	Died	Patient had a short remission of ALS—died with bulbar involvement
Reys (1925)	F	16	4	1	None	Progressive	L. upper limb affected with encephalitis—also site of ALS onset
Carr (1926)	M	22	< 1	7	None	Progressive	
Guillain and Alajouanine (1926)	F	35	2	1.5	Severe 'contracture extrapyramidale'	Progressive	Simultaneous onset of extrapyramidal and ALS signs
Jancsó (1928)	F	40	< 0.1	1.2	'Extrapyramidale symptome'	Died	
Wimmer and Neel (1928)							
Case 2	M	36	0	no follow-up	'Agitation choreiforme'	No follow-up	CSF pleocytosis
Case 3	M	47	0	2	Parkinsonism	Died	Parkinsonism onset later than ALS; CSF pleocytosis; CNS perivascular mononuclear cells
Case 9	M	20	5	1	None	Progressive	Possible onset of ALS at time of encephalitis (aged 20 yrs)
Case 16	M	36	0.5	3	Parkinsonism	Died	CNS perivascular lymphocytes
Case 17	F	34	3	4	None	Died	Suspected encephalitis only; CNS perivascular mononuclear cells
Salus (1929)	F	30	1	2	None	Progressive	
Ornsteen (1930)	M	45	< 0.1	0.5	None	Progressive	Bulbar onset
Illing (1932)	F	30	7	3	Parkinsonism	Progressive	Parkinsonism onset four years after encephalitis
Decourt, Mathieu and Meyer (1934)	F	17	12	3	Parkinsonian rigidity	Progressive	Parkinsonism onset probably twelve years after encephalitis
Lhermitte, Thibault and Ajuriaguerra (1938)	M	23	7	6	Parkinsonism	Died	Parkinsonism onset within five years after encephalitis
Milhorat (1946)							
Case 1	M	49	17	4	Parkinsonism	Died	Simultaneous onset of parkinsonism and ALS
Case 2	M	15	9	8	None	Progressive	
Roger and Cain (1947)							
Case 1	M	19	18	8	Parkinsonism	Died	Parkinsonism onset seventeen years after encephalitis; hypoæsthesia on side of atrophy and parkinsonism
Case 2	M	37	28	—	Parkinsonism	Progressive	Parkinsonism onset twenty-one years after encephalitis
Betz (1952)	F	15	13	14	Hemiparkinsonism	Progressive	Parkinsonism onset fourteen years after encephalitis
Greenfield and Matthews (1954)							
Case 1	M	18	22	4	Parkinsonism	Progressive	Parkinsonism onset ten years after encephalitis
Hufschmidt, Schaltenbrand and Solcher (1960)							
Case 1	M	23	24	0.5	Parkinsonism	Died	Parkinsonism onset twenty-two years after encephalitis
Case 2	M	12	19	20	Extrapyramidal features	Progressive	Extrapyramidal onset seven years after encephalitis
Hirano and Zimmerman (1962)	M	28	30	4	Parkinsonism	Died	Parkinsonism onset sixteen years after encephalitis
McMenemey *et al.* (1967)	F	20	31	6	Parkinsonism	Died	Parkinsonism onset twenty-five years after encephalitis

* CSF = cerebrospinal fluid; CNS = central nervous system.

The case of Hirano and Zimmerman (1962) showed loss of anterior horn cells but no degeneration of the pyramidal tracts. Severe neuronal loss with numerous examples of neurofibrillary changes was evident in the substantia nigra. While neurofibrillary tangles were not seen in the cerebral cortex they were present in small numbers in the hypothalamic nuclei, substantia innominata, periaqueductal grey matter and the reticular formation of the brain stem.

McMenemey *et al.* (1967) observed more extensive degenerative changes in their case of ALS-parkinsonism. There was degeneration in the pyramidal pathway and the medial part of the fasciculus gracilis of the posterior columns. Loss of neurons was seen in the head of the caudate nucleus, globus pallidus, thalamus, substantia nigra, locus caeruleus, periaqueductal grey matter and other neuronal structures in addition to the anterior horn cells. Neurofibrillary degeneration was found in various groups of neurons such as the parietal cortex, hippocampal gyrus, hippocampus, globus pallidus, periaqueductal grey matter and, rarely, the anterior horn cells. Granulovacular degeneration was also seen in an anterior horn cell.

WESTERN PACIFIC ALS

(*i*) *Clinical findings*. There have been a number of reports of ALS occurring with an extraordinary high incidence in small foci in the Western Pacific region. Located, mainly, on Guam and the Kii Peninsula in Japan they have been extensively reviewed (Stanhope, Brody and Morris, 1972; Reed and Brody, 1975; Kurland and Brody, 1975; Yase, 1972; Shiraki and Yase, 1975) and require little discussion. A focus in New Guinea has been discovered recently by Gajdusek (1979).

Guamanian ALS occurs in individuals of Chamorro ancestry and prior to 1965 the average annual incidence rate for males was over 50 per 100000 and for females in excess of 20 per 100000 population (Reed and Brody, 1975). By 1972 this incidence had fallen by 50 per cent. The male to female ratio is 1.8:1 and the mean age of onset is 46 years with a duration of about four years. The data for the Kii Peninsula are similar (Yase, 1972). Clinically, the disease is remarkably similar to classical ALS. Parkinsonism and dementia are found in the same population in both regions with about the same incidence as ALS. The dementia and parkinsonism have a marked tendency to occur together and they may occur in individuals who are affected with ALS. About 7 per cent of the total of all ALS, dementia and parkinsonism patients show, clinically, a combination of the three conditions (Stanhope *et al.*, 1972). Gajdusek (1979) also has found a combination of basal ganglia symptoms and progressive dementia with ALS in the New Guinea focus.

(*ii*) *Pathological findings*. Hirano, Malamud, Elizan and Kurland (1966) observed in pathological studies on 34 Chamorros who died of ALS a severe loss of anterior horn cells in all cases, degeneration of the pyramidal tracts in over 90 per cent of cases and complete sparing of the posterior columns and spinocerebellar tracts in all cases. Neuronal loss and/or neurofibrillary degeneration were found throughout the brain and spinal cord, notably the frontotemporal cerebral cortex, hippocampus, substantia nigra, locus caeruleus, dentate nucleus and anterior horn cells. There was also granulovacuolar degeneration in the pyramidal cells of Ammon's horn. It is also important to note that Anderson, Richardson, Okazaki and Brody, (1979) found neurofibrillary degeneration in the normal Chamorro population occurring at an earlier age than has been reported for comparable populations elsewhere. The distribution of the neurofibrillary changes is similar in the ALS, parkinsonism-dementia and normal subjects. In some normal subjects granulovacuolar changes are present in the hippocampus.

The findings in the Kii Peninsula cases are similar to those found on Guam. Hirano *et al.* (1966) believe that ALS and parkinsonism-dementia are manifestations of a single disease entity.

CREUTZFELDT-JAKOB DISEASE

Lower motor neuron and pyramidal tract degeneration occur as part of widespread abnormalities of the nervous system in Creutzfeldt-Jakob disease. The predominant features are dementia and behavioural disturbances and symptoms referable to the cerebellar and visual systems. In the clinical course, movement disorders, including myoclonus late in the disease, appear in almost all cases and tend to be trembling and choreo-athetoid in type (May, 1968; Roos, Gajdusek and Gibbs, 1973; Masters and Richardson, 1978; Brown, Cathala, Sidowsky and Gajdusek, 1979). An 'amyotrophic type' of this disease has been described.

(*i*) *Clinical findings.* Seven case reports of spastic pseudosclerosis or Creutzfeldt-Jakob disease of the 'amyotrophic type' were reviewed (Davison, 1932; Davison and Rabiner, 1940; Jervis, Hurdum and O'Neill, 1942; Stengel and Wilson, 1946; Allen, Dermott, Connolly and Hurwitz, 1971; Sherratt, 1974). All were males with a mean age of onset of 47 years and the duration of illness was two years. None resembled the classical form of Creutzfeldt-Jakob disease described above but rather ALS-dementia or ALS-dementia-parkinsonism which was discussed earlier. It is noteworthy that van Rossum (1968) in a review of Creutzfeldt-Jakob disease, summarized his view of the 'amyotrophic type' of the disease by stating that, clinically, these cases often suggest amyotrophic lateral sclerosis with dementia and histologically the changes are similar, including degeneration of the cortex, the neostriatum, the pyramidal tract and the anterior horn cells. Masters *et al.* (1979) have stated that 'the entity of amyotrophic Creutzfeldt-Jakob disease may be a variant of amyotrophic lateral sclerosis; it has not yet been transmitted to animals'.

(*ii*) *Pathological findings.* The findings in the 7 cases were similar. Lower motor neuron and pyramidal tract degeneration were present in all cases with posterior column degeneration in 2 cases. Cerebral cortical degenerative change was seen in all cases and was prominent in the frontotemporal region. Loss of neurons and gliosis were seen particularly in layer 3 and less often in layers 5 and 6 of the cerebral cortex. Other structures showing neuronal loss, including caudate nucleus, putamen, globus pallidus, substantia nigra, were observed in all subjects. Alzheimer neurofibrillary tangles were seen in the cortex in one case while in another there was a moderate number of senile plaques. The pathological findings, in general, were similar to the syndrome of ALS, dementia and/or parkinsonism described earlier.

DISCUSSION

There has been the longstanding view that the lesions in the nervous system in ALS are limited to the upper and lower motor neurons but as Brownell *et al.* (1970) have stated, '. . . motor neurone disease is not merely a simultaneous degeneration of upper and lower motor neurones. It may involve either more or less than these two systems, and the relative severity of the lesions in different structures varies from case to case.' Like the degeneration of the posterior columns, Clarke's columns and spinocerebellar tracts in classical familial ALS, lesions outside the upper and lower motor neurons are usually clinically silent. Often they are relatively minor but occasionally the impairment is severe with the appearance of clinical signs. For example, cerebral cortical degeneration is seen in some members of families with ALS without dementia but in others the lesions are more striking with the presence of marked dementia (15 per cent of families). In such cases it seems likely that dementia is part of the ALS syndrome. It is possible that ALS-dementia in sporadic ALS is the counterpart of ALS-dementia seen in the familial disorder. In addition to the cerebral cortex, other parts of the nervous system such as the corpus striatum, globus pallidus and substantia nigra may be affected with a degree of severity in some cases that results in extrapyramidal signs characteristic of parkinsonism. The ALS-parkinsonism-dementia complex is, therefore, not exclusively a disorder found in the Western Pacific but a universal condition.

It is proposed that dementia and parkinsonism when associated with sporadic or familial ALS are simply variants of classical ALS and the classical syndrome varies from case to case depending on other factors such as the genetic predisposition of the individual. This may be the case in the Guamanian form wherein there appears to be an unusual propensity for ALS, dementia and parkinsonism to occur in the Chamorro population. Evidence in support of this is the finding of neurofibrillary degeneration to a greater than usual degree in the normal Chamorro population.

The role of infection in post-encephalitic ALS raises the possibility of an infective ætiology in the other forms of the disease. Post-mortem information in post-encephalitic ALS is limited but, as noted by Greenfield and Matthews (1954), neurofibrillary changes found in this condition have been a common finding in the pigmented cells of the brain-stem in post-encephalitic parkinsonism. These authors, like some earlier workers, regard the neurofibrillary changes as evidence of a prolonged toxic effect related to virus infection. This is of particular interest in view of the presence of these alterations in both post-encephalitic and Guamanian ALS.

ALS has not been transmitted to animals nor does it have the suggestive features of a persistent virus infection such as inflammatory foci in the nervous system or spinal fluid changes. Nevertheless, a viral ætiology has been suspected and poliovirus, in particular, has been investigated, although without success, even in a patient with ALS with a history of poliomyelitis who had an autopsy examination and detailed virological studies (Roos, Viola, Wollmann, Hatch and Antel, 1980). Isolating a virus or transmitting it to experimental animals can be difficult, as was the case in subacute sclerosing panencephalitis which required the co-cultivation of cultured brain tissue with permissive cells to recover the virus (Baublis and Payne, 1968). Also, host susceptibility may have an important role as in the patient with immunodeficiency described by Davis, Bodian, Price, Butler and Vickers (1977) who developed an ALS-like picture following the administration of an attenuated poliovirus vaccine. If ALS has an infective ætiology the slow masked infections caused by conventional, possibly defective, viruses may provide the best lead if the appropriate conditions for study can be found (Gajdusek, 1977).

While classical ALS is almost always a disease of adult onset there are reports which suggest that it may rarely occur sporadically in children. Familial ALS in the child, however, is probably a different disorder from classical ALS in view of an appearance of autosomal recessive inheritance, prolonged survival and, in one case, severe pathological alterations in the white matter.

It appears likely that the ALS form of Creutzfeldt-Jakob disease is the same condition as the sporadic type of ALS-dementia or ALS-dementia-parkinsonism that has been described by a number of authors. As suggested by Masters *et al.* (1979) this may be a variant of classical ALS rather than a variant of Creutzfeldt-Jakob disease. Evidence has been presented that supports this concept for ALS that is accompanied by dementia and/or parkinsonism, generally.

Finally, sporadic and familial ALS of adult onset requires careful comparative evaluation since it is possible that they are different entities in view of the marked involvement of the posterior columns, Clarke's column and spinocerebellar tract in the familial condition in contrast to sporadic ALS.

SUMMARY

Sporadic and familial classical amyotrophic lateral sclerosis (ALS) have, by definition, clinical features that are due solely to degeneration of the upper and lower motor neurons. However, 15 per cent of families with classical ALS have one or more affected members who also show dementia, and pathological changes can be found in both classical sporadic and familial cases in the cerebral cortex, corpus striatum, globus pallidus, thalamus, substantia nigra and other regions.

Although sporadic and familial classical ALS are clinically indistinguishable, degeneration of the posterior columns was present in 80 per cent of families (70 per cent of autopsies) compared with less than 10 per cent in sporadic ALS. Similarly,

degeneration of Clarke's column was seen in over half the cases of posterior column degeneration in familial ALS but in none of the cases of sporadic ALS.

In a review of 42 cases of sporadic ALS accompanied by dementia and/or parkinsonism both the dementia and parkinsonism had the same mean age of onset as ALS which suggests that all three conditions are part of the same process. Pathological studies of the nervous system in these cases showed a high incidence of pyramidal tract and a low incidence of posterior column degeneration which were similar to classical sporadic ALS. Patients with ALS-dementia and ALS-dementia-parkinsonism showed more striking cortical and subcortical neuronal degenerative changes than are found in classical ALS that reflected the dementia and extrapyramidal features.

Four cases of sporadic ALS beginning in childhood have been described with a mean age of onset of ALS of 14.5 years and duration of sixteen months. The pathological findings in 3 of the cases included abundant intracytoplasmic basophilic neuronal inclusions and in 2 cases these were seen throughout the nervous system. Familial ALS beginning in childhood, in contrast to an autosomal dominant pattern in the adult, appears to have an autosomal recessive mode of inheritance and has a much longer life expectancy of fifteen or more years. These and other clinical features and a single pathological study suggest that this is a different entity from adult ALS.

Post-encephalitic ALS which followed encephalitis lethargica occurred in combination with parkinsonism in two-thirds of cases. Pathological changes in the nervous system showed neuronal loss and neurofibrillary degeneration in various groups of neurons throughout the nervous system in 2 autopsy cases.

Parkinsonism and dementia may accompany the Western Pacific forms of ALS (Guam, Kii Peninsula and New Guinea) in addition to occurring separately. Neuronal degeneration and neurofibrillary change in the cortex, subcortical and brain-stem nuclei and spinal cord has been found in both ALS and the parkinsonism-dementia cases and, on Guam, in the normal (Chamorro) population.

From the accounts of the 'amyotrophic form' of Creutzfeldt-Jakob disease the disorder is clinically indistinguishable from the cases that are described as ALS-dementia or ALS-dementia-parkinsonism. Pathological findings also are similar with cortical, subcortical, brain-stem and spinal cord neuronal degeneration and gliosis.

ACKNOWLEDGEMENTS

The author is grateful to Drs Valentine Donish, William Ross, Roland Auer, Carmelo Tarano and Ryoichi Nakamura, for their assistance in translation. Also to Dr John Kaufmann, for pathological examination of the two personal cases.

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(*Received September 17, 1980*)

Brain (1981), **104**, 249-277

HELWEG'S TRIANGULAR TRACT IN MAN

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INTRODUCTION

OUR knowledge of the anatomy and function of individual tracts in man is usually amplified and confirmed from experimental work on animals. A notable exception is the triangular tract named after Helweg who first described it in detail (1888). This tract is striking and unmistakable in the human cord, but a definite homologue for it has not been identified in any other species. The tract is present in the caudal part of the medulla and at least the first five cervical segments, lying on the periphery of the anterolateral sector. The origin, termination and polarity of the fibres are undecided. A relationship with the olive has been assumed, because the cranial termination of the tract is in the neighbourhood of the lower third of the olive and the term 'olivospinal' has been commonly applied to it since 1894 (von Bechterew). More recently, the finding of spino-olivary fibres in the cat has led to the view that the fibres of Helweg's tract might be spino-olivary (Brodal, Walberg and Blackstad 1950). It must be emphasized that no connection between cells of the olive and the fibres of Helweg's tract in man, either as giving origin to the fibres or of receiving their termination, has ever been demonstrated.

Helweg's tract is unique among the long descending and ascending tracts in the spinal cord because it consists mainly, possibly entirely, of extremely fine fibres. In Weigert Pal preparations it therefore stands out as an area of pallor in the anterior column of the cervical cord and in the lower medulla. The triangular shape of this unstained area in transverse sections of the upper cervical segments gave rise to its name 'triangular tract'.

In the last two decades of the nineteenth century and the first two of the twentieth, a considerable number of workers reported their findings on Helweg's tract. Their observations were limited by the histological methods available at the time—Weigert Pal, carmine and Marchi. These methods are applicable to the study of myelinated fibres only, and the amount of myelin present in Helweg's tract is small. Some larger myelinated fibres are present in the territory of the tract, but most, if not all, of these belong to neighbouring tracts. It seems likely that some of the early

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observations were based on these unrelated fibres. The early papers on Helweg's tract were reviewed by Nathan and Smith (1955). Few have been published more recently, with the notable exception of excellent papers from Kyoto, in particular from Okamoto and his colleagues (Okamoto, Kusaka, Katayama and Hattori, 1955; Okamoto, 1966; Mizuno, Yoshida and Okamoto, 1968; Mizuno, Nakamura and Okamoto, 1968). The Japanese incline to the view that the tract is mainly ascending, arising from the anterior grey matter, basing their conclusions largely on the study of brains in which there was degeneration of the olive and on anencephalic fœtuses. On the other hand, Sie (1956) in his study of tracts in the medulla and first cervical segment in man, based on degeneration after various lesions, considered the tract to be descending.

In regard to the size of the fibres of the tract, Okamoto (1966) made an analysis of their calibre in Weigert Pal material. He estimated that 80 to 90 per cent of the fibres measured less than 3 μm, some of them being stained by the Weigert Pal technique, but the majority remaining unstained; 53 per cent of these fine fibres were found to be less than 1 μm, and 35 per cent 1 to 3 μm; 11 per cent measured 4 to 10 μm, and 0.4 per cent 11 to 17 μm. It is to be noted that almost every paper on Helweg's tract has been based on stains which only show the myelin, Weigert Pal and, more rarely, Marchi preparations; Sie's thesis is the exception, being based on Häggqvist preparations, in which both myelin and axons are stained.

The surprisingly little interest shown in Helweg's tract today seems to be due to two causes. First, the tract is shown up much more vividly in sections prepared by the Weigert Pal method than in most other preparations. Decreasing use of this method results in few histologists becoming interested in the tract. Second, no definite homologue of the tract in species other than man has so far been recognized (Okamoto 1966), and so experimental investigations on it are not possible.

This paper presents observations on:

(1) the normal anatomy of Helweg's tract, including an analysis of the very fine fibres which form the bulk of the tract. These fibres have been shown by three methods not previously applied to the tract: by a silver impregnation method showing up very fine fibres, by the use of epon-embedded semi-thin sections, and by electron microscopy;

(2) the significance of the appearance of the normal Helweg's tract in interpreting degeneration in the cervical cord;

(3) the origin of other larger fibres in the tract;

(4) the relationship between Helweg's tract and other tracts;

(5) the practical implication of Helweg's tract in respect to the location of the spinothalamic complex in the operation of cervical spinothalamic cordotomy;

(6) the polarity of the fine fibres;

(7) the absence of any relationship between Helweg's tract and the olive or the central tegmental tract.

MATERIAL AND METHODS

Material

Observations on Helweg's tract are part of an extensive study of the anatomy of the white matter in the anterior and lateral columns of the human cord. A large amount of material has therefore been available for examination with special interest in this tract. In the majority of cases, sections from all segments of the cervical cord and of the medulla were examined. Where relevant, sections from the rest of the cord were also examined.

There were 35 cases in which the cords were normal or had lesions unconnected with anterolateral columns, at least on one side; 9 cases with lesions of the anterolateral column involving the region containing Helweg's tract; 22 cases with supraspinal lesions of which 16 involved the cerebral hemispheres, 2 the midbrain, 3 the pons, one the inferior olivary nucleus; 10 cases of motor neuron disease.

Methods

(1) Numerous sections from all levels of the material were prepared by a wide variety of neurohistological methods. In most instances, celloidin embedding, in a few, wax, was used. Frozen sections were also taken. Methods included: Weigert Pal, Loyez, Weil, Luxol-fast blue, Häggqvist, Marchi, Sharlach R, phosphotungstic acid hæmatoxylin, thionin, hæmatoxylin and eosin, hæmatoxylin and van Gieson, Nauta, Gros-Bielschowsky, and Marsland, Glees and Erikson's method for silver impregnation of axons (original method and modifications).

Consistently good silver impregnations for axons were achieved only after long experimentation with modifications of different silver methods which were not giving satisfactory results in human material after very prolonged storage. We have found a Marsland, Glees and Erikson's method (original method, Marsland, Glees and Erikson, 1954) for wax-embedded material, modified for celloidin by Terruli (1975) and further modified in our laboratory to give good results even on old, long-fixed material (technical paper on method by Ursula Starega, in preparation). Once this technique had been developed, old material and blocks were re-sectioned and prepared by the method.

No conclusion about the normality of Helweg's tract were drawn unless satisfactory axon preparations were available.

(2) In 2 cords, blocks from C3 were processed for semi-thin sections and electron microscopy. The tissue was fixed in 3 per cent buffered glutaraldehyde, post-fixed in 1 per cent osmium tetroxide, dehydrated in ascending grades of alcohol and embedded in epon. Semi-thin sections were cut at 1 μm and stained with toluidine blue. Sections for electron microscopy were cut on a Reichert Ultracut ultramicrotome and stained with lead citrate and uranyl acetate.

Semi-thin sections were taken, from both cords, of Helweg's tract and of other tracts, for comparison of the fibre calibre. Electron micrographs were taken of the entire Helweg's tract in one cord.

These sections were prepared in Dr David Landon's department and the electron micrographs were examined by him. We are greatly indebted to Dr Landon and his staff for this invaluable help.

We should like to make a comment on the methods on which the present series is mainly based. The silver method used was modified successfully for human material in our laboratory only recently, and was then applied to the material which had previously been examined histologically by other methods. The method has been most useful in its clear demonstration of fine axons, and sections prepared by it have been the main basis for the observations.

Two recently acquired normal cords were specifically processed for the examination of Helweg's tract in semi-thin and ultra-thin sections. These have given invaluable detailed information regarding the spectra of fibres composing the tract. It would be of the greatest interest if similar sections could be obtained from cases in which there had been lesions of Helweg's tract, so that changes due to the lesion could be identified and assessed in respect to the different kinds of fibre seen in the normal. In such material, if the survival period were appropriate, sections could also be prepared by the Nauta or similar method to study the termination of the degenerating fibres.

The chance of such human material being examined in this way depends on many factors. The cord has to be normal apart from the operative lesion. The survival between operation and death must not be so short that few results of transection would be histologically visible, nor so long that there might be shrinkage and gliosis which would obscure the picture of fibre degeneration. The cord and medulla would have to be removed without much delay after death by a pathologist interested in neuroanatomy, and blocks would have to be fixed by a method suitable for ultramicroscopy. The processing and interpretation of the sections would have to be done by those skilled in such methods.

Most of these factors have been influential in deflecting neuroanatomical work from human to experimental animal material, even for ordinary histological studies. They are even more difficult to satisfy in respect to ultramicroscopy, but efforts should be made to do so, for therein must lie the answers to many neuroanatomical queries.

OBSERVATIONS

Anatomy of Helweg's Tract

In all the normal cords, with two exceptions, we have recognized Helweg's tract on both sides, when appropriate staining techniques were applied. In one cord, for no reason that we could determine, we could not find the tract on either side. In another cord, discussed later, we could identify the tract on one side only.

The classical appearance of the tract in Weigert Pal preparations is shown in fig. 1. The tract is strikingly pale, in contrast to the rest of the section. C2B is a negative print of C2A, in which myelin-poor areas appear black and show up particularly well. Throughout its course the tract lies on the periphery, or separated from it by a few fibres. It is largest in the lower medulla and fades out usually about C5, although occasionally a few fibres are present in C6 or C7. The outline of the tract is characteristic and different at different levels. In the medulla (M) it is bun-shaped. In the upper cervical cord, shown here in C2, it is triangular, broader in its posterior part, tapering anteriorly, its medial border lying parallel to the lateral border of the anterior horn. In the mid-cervical cord, C4, the tract is small and narrow, shaped like a half-lens. It is still present in the lower cervical cord, C7, of this cord, in the shape of a narrow band. Throughout its spinal course, anterior nerve roots cross the

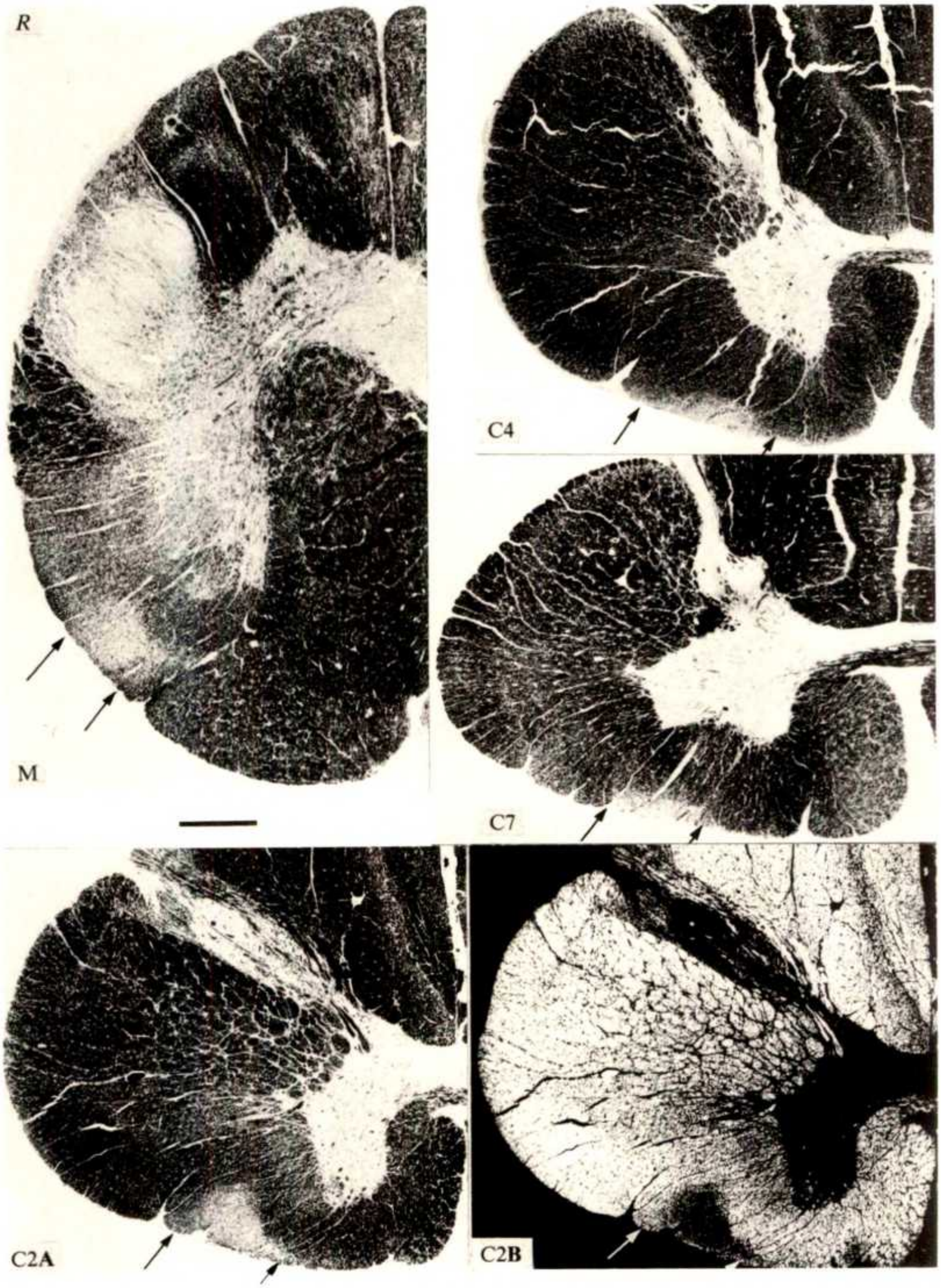

FIG. 1. Sections from medulla (M) and cervical segments (C) of normal cords showing appearance of Helweg's tract at different levels. Fig. C2B is a negative print of fig. C2A. (Weigert Pal preparations. Bar = 1 mm.)

tract obliquely. Occasionally the tract is larger than usual, with a long tail extending anteriorly.

Other regions of pallor, although less striking than that of Helweg's tract, can be seen in the sections. There is a diffuse pallor of the white matter close to the anterior horn, especially along its lateral border. This is seen here most clearly in C2A and in the negative print C2B. This is a normal appearance due to the presence of numerous fine fibres in this region. In these sections of C2 there is a narrow band of pallor in the medial aspect of the fasciculus gracilis; this is due to degeneration of ascending fibres from a posterior nerve root involved in tumour. The ease with which the normal pallor of Helweg's tract could be mistakenly interpreted as indicating degeneration is shown more vividly in fig. 2. In this cord, the right Helweg's tract is normal. On the left, there is degeneration of ascending fibres shown as pallor, due to an anterolateral cordotomy lesion in the segment below. Helweg's tract is included in the pale area on this side. If the extent of the cordotomy had not been known from the sections containing the lesion, it would not have been obvious whether the lesion had included Helweg's tract or not. Further, if the normal appearance of Helweg's tract is not known, the pallor on the left side, as well as that on the right, could have been interpreted as indicating degeneration.

Under higher magnification, fig. 3, C2, Helweg's tract can be seen in Weigert Pal preparations to contain scattered, myelinated fibres of varying diameter, especially near the borders of the tract and on the periphery, but the dominant characteristic is of general poverty of myelin staining, so that the number of fibres stained is small.

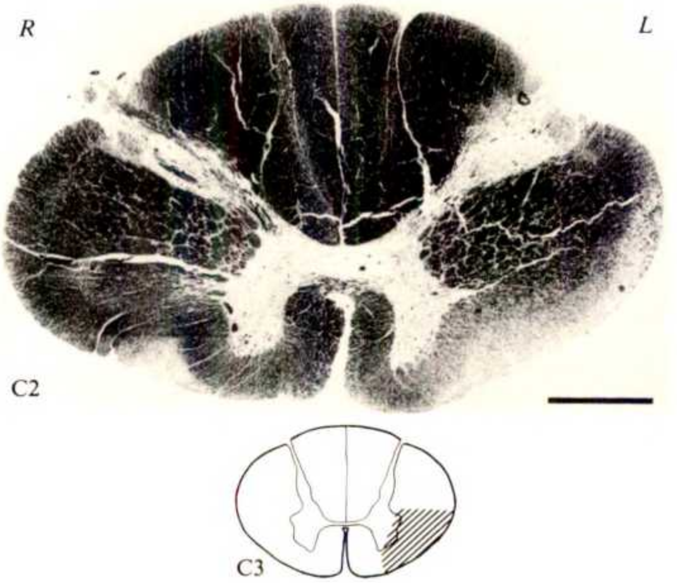

FIG. 2. Section of C2 showing normal appearance of Helweg's tract on right side, and ascending degeneration, due to anterolateral cordotomy, including area of Helweg's tract, C3. (Weigart Pal preparation. Bar = 2 mm.)

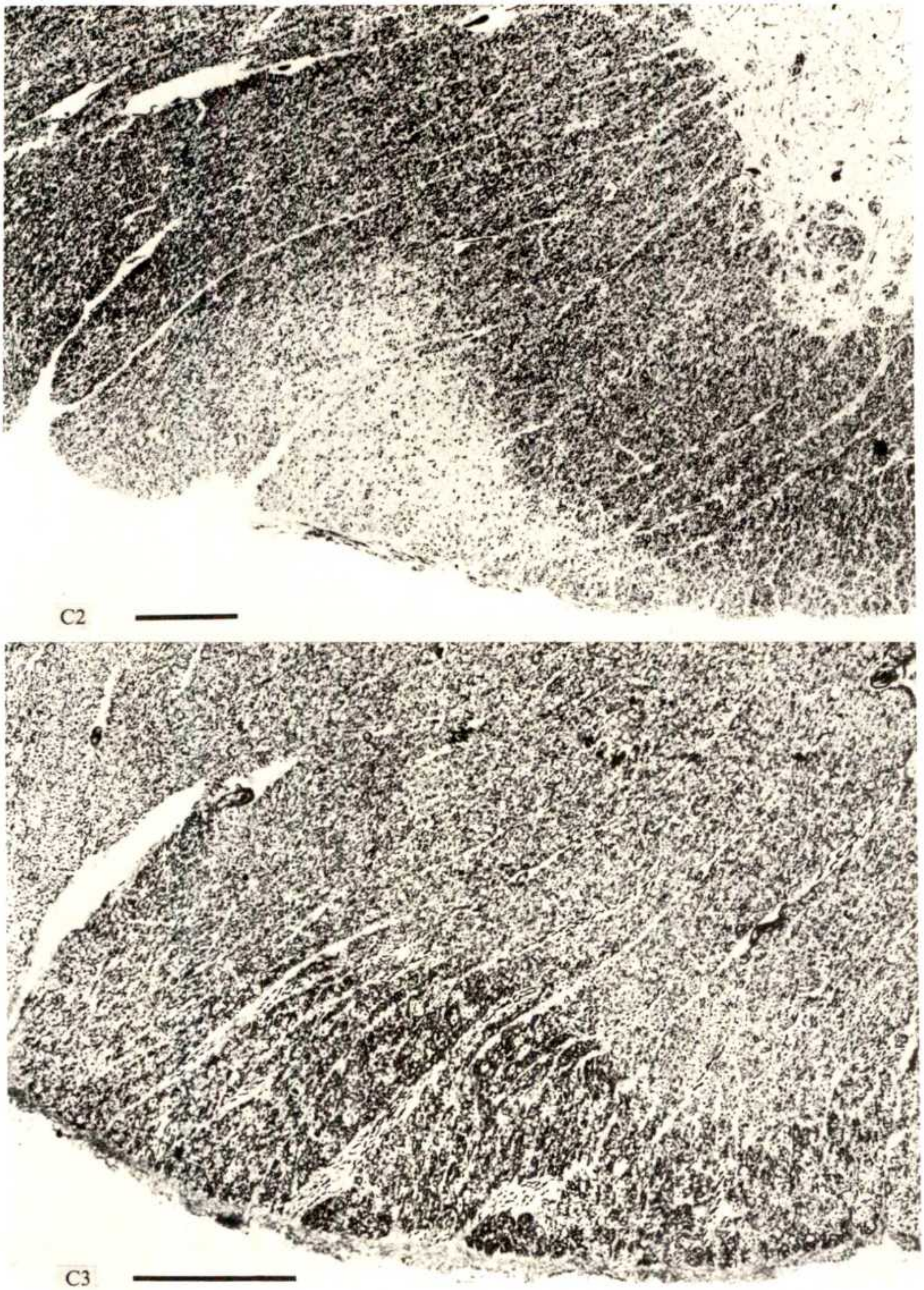

FIG. 3. C2 shows myelinated fibres within normal Helweg's tract, pallor of tract nevertheless a dominant feature. (Weigart Pal preparation. Bar = 0.3 mm.) C3 shows intense dark appearance of normal Helweg's tract due to closely packed axons. Some larger fibres also present. Anterior nerve roots are seen crossing tract. (Marsland, Glees and Erikson silver impregnation method for axons: modified. Bar = 0.3 mm.)

This is in marked contrast to the appearance in silver preparations showing axons, fig. 3, C3. In these preparations, the tract stands out as a clearly defined dark area because of the large proportion of very fine fibres in it. This appearance is unique in the spinal cord. The only other tract consisting largely of very fine fibres is Lissauer's tract, but in that tract they do not appear to be so densely packed.

The distinctive appearance of Helweg's tract in axon preparations is shown by comparing it with other tracts, for instance the spinocerebellar and corticospinal tracts. The appearance of the spinocerebellar tract is characterized by a high proportion of very large fibres, shown in fig. 4A, and very few fine fibres. The thick myelinated sheaths around the axons are unstained. The appearance of the corticospinal tract, shown in fig. 4B, is characterized by larger myelinated fibres of varying calibre and numerous small fibres which are mainly in groups among the larger fibres. The appearance of Helweg's tract, fig. 4C, is clearly different. There is a considerable number of obviously myelinated fibres: the calibre of these varies from large to very small. But the majority of the fibres present are shown only as axons, and it is the large number and close packing of these axons that give the tract its characteristic appearance, making it easily distinguishable from all other tracts in the cord.

More details of the component fibres of Helweg's tract are shown in the semithin (1 μm) sections, fig. 5, and in electron micrographs, fig. 6. The striking features of these sections are that there is a very large number of fine fibres present, that the fibres all appear to be myelinated, even the finest fibres, and that in many instances the myelin sheath is extremely thin. As it had been anticipated that the main characteristics of the tract would be the presence of many non-myelinated fibres, these were searched for in the EM sections. Dr Landon reported that there is an almost complete absence of non-myelinated fibres. He considered that 'although some very small non-myelinated fibres could be overlooked, they constitute an almost insignificant proportion of the total'.

Preliminary measurements of the diameters of the fibres in the tract have been made manually on electron micrographs at magnifications of 8000; 800 fibres were measured. These suggest that the fibres range from 0.37 μm to 17 μm. The majority, 77.5 per cent, measure between 0.37 μm and 2.5 μm. In many of these, 47.5 per cent, the thinness of the myelin sheath is such that the diameter of the whole fibre is only minimally larger than that of the axon. A smaller number, 30 per cent, of fine fibres stand out because the proportion of myelin to axon is much greater. These measure 1 μm to 1.5 μm. In many, the total diameter (D) is approximately three times the diameter of the axon (d). The g ratio (d/D) within all the fine fibres varies between 0.29 μm and 0.89 μm. Larger myelinated fibres are also present. Most of these range in total diameter from 2.51 μm to 6.5 μm. They form about 21 per cent of the total. A very small number, 1.5 per cent, measure 6.51 μm to 17 μm. All these larger myelinated fibres will be considered in the next section.

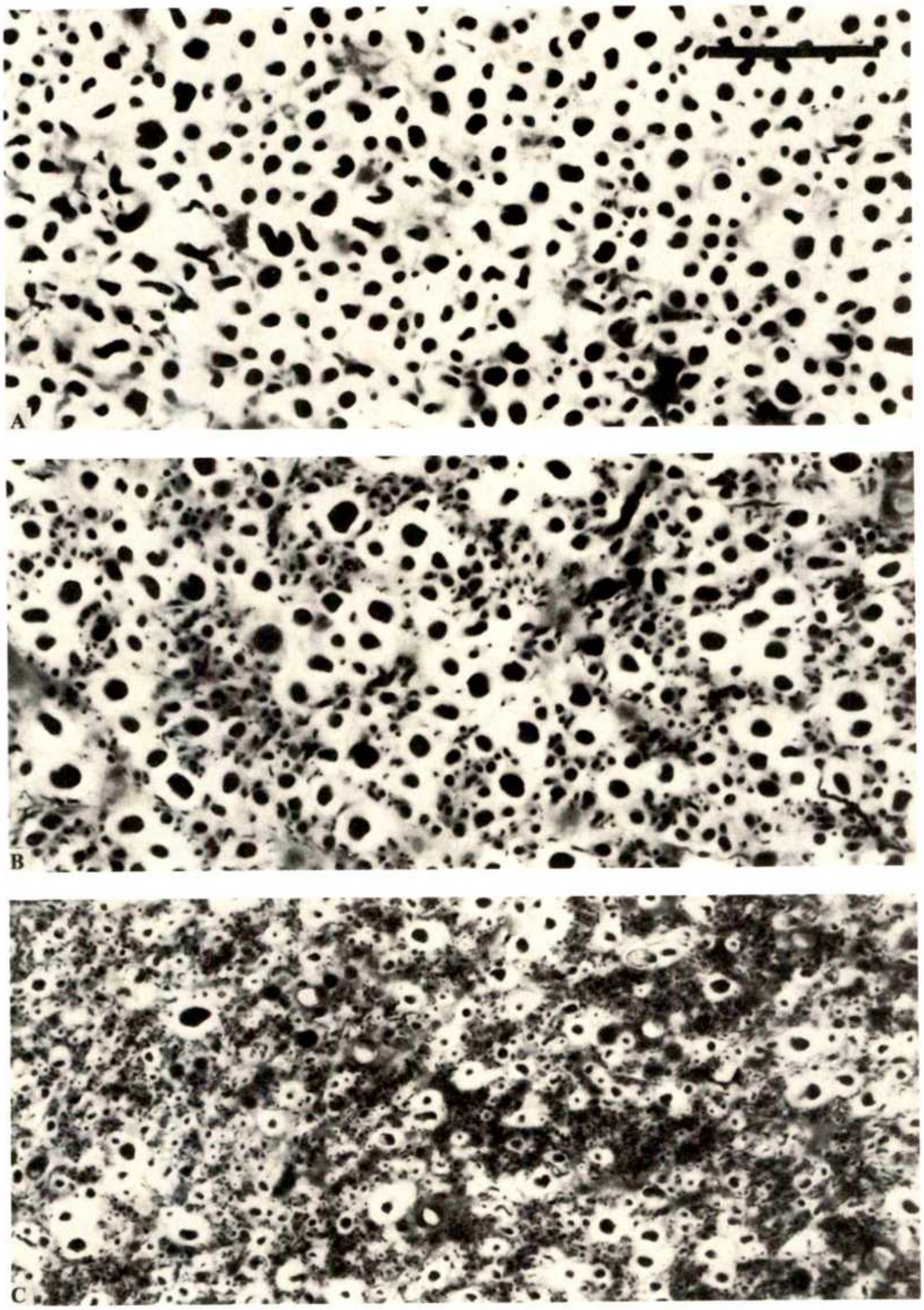

FIG. 4. Axon preparations of different tracts showing characteristic fibre patterns—myelin sheaths pale. A. Posterior spinocerebellar tract: mainly large myelinated fibres. B. Lateral corticospinal tract: myelinated fibres of varying calibre, numerous small myelinated fibres, mainly in groups. C. Helweg's tract: very numerous small fibres, without obvious myelin sheaths, many in large tightly packed groups; myelinated fibres of widely varying calibre scattered among them. (Marsland, Glees and Erikson: modified. Bar = 50 μm.)

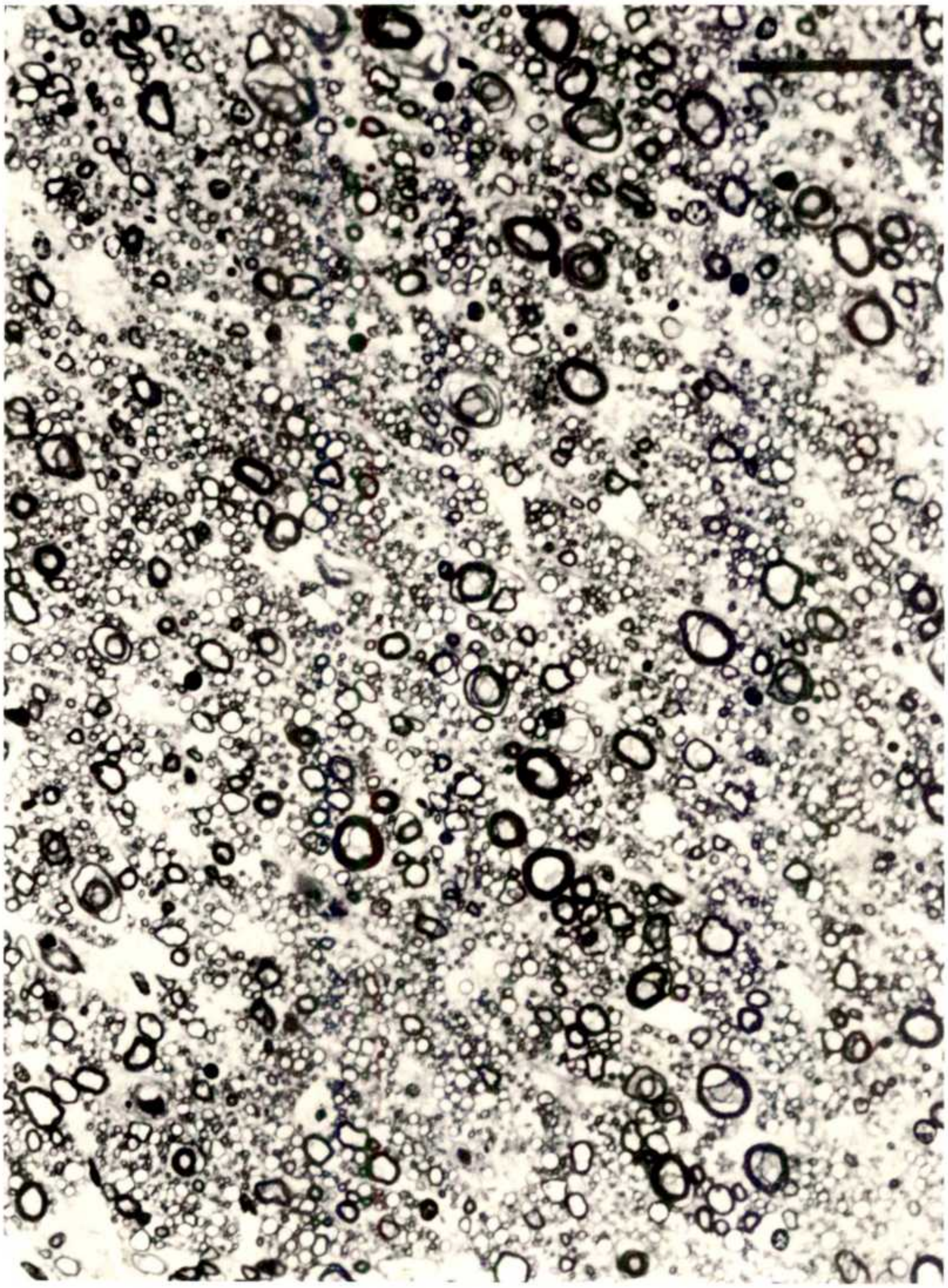

FIG. 5. Semi-thin (1 μm) sections of normal Helweg's tract. Predominant fibres are fine, of varying calibre, with very thin myelin sheaths. A small number of fine fibres with much thicker myelin sheaths are present, and also larger well myelinated fibres. (Epon embedded: toluidine blue. Bar = 50 μm.)

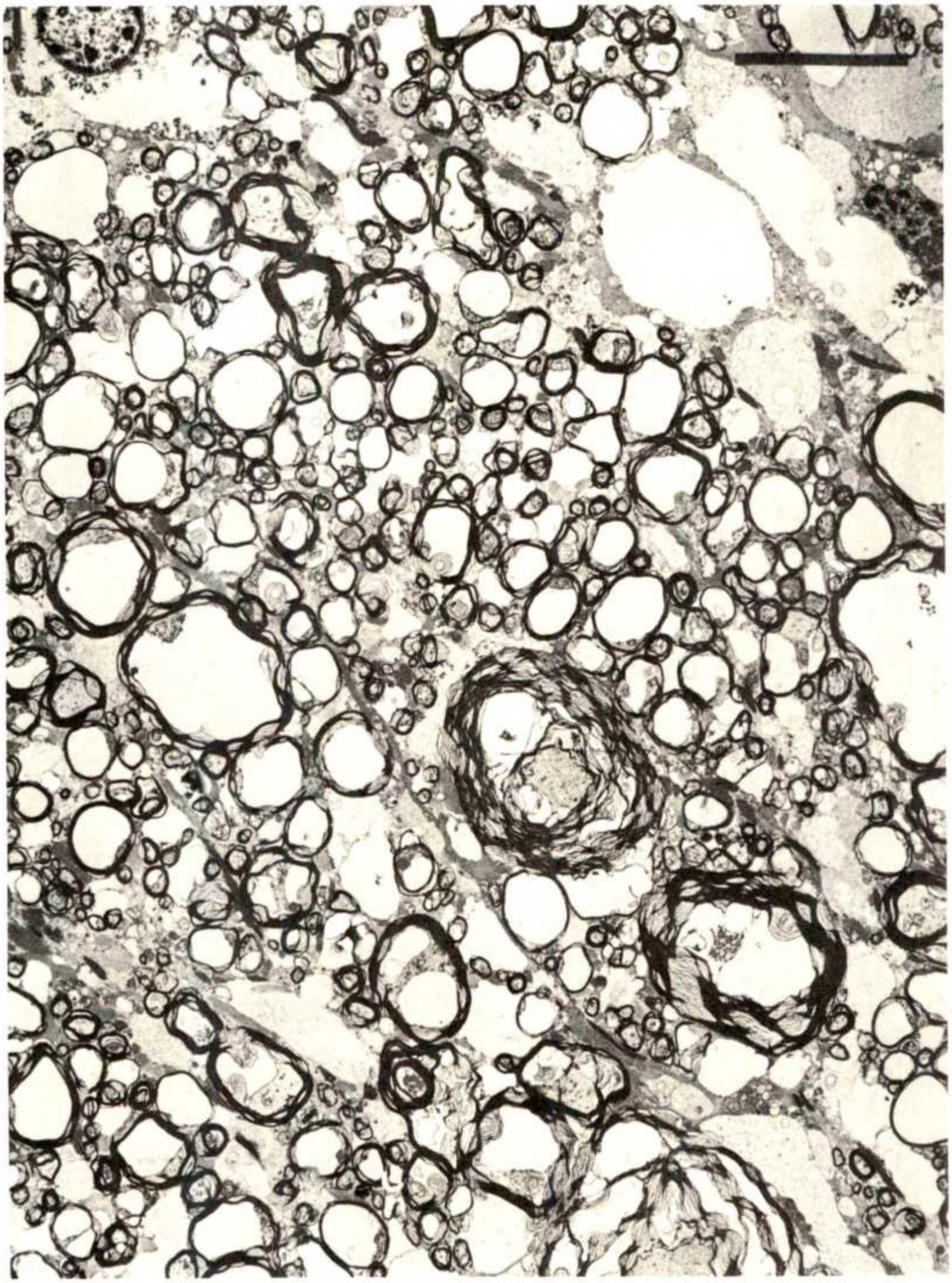

FIG. 6. Electron micrograph of normal Helweg's tract. Majority of fibres characterized by fineness and thin myelin sheaths, total diameter varying between 0.5 μm and 12.8 μm. Non-myelinated fibres absent. (Uranyl acetate and lead citrate. Bar = 10 μm.)

Relationship of Helweg's Tract to Other Tracts and the Origin of the Larger Myelinated Fibres Within the Tract

The topographical relationship between Helweg's tract and other tracts near it were established by plotting the location of these tracts in cases in which they were degenerating. This material also allowed deductions as to the origin of the larger myelinated fibres within Helweg's tract. In one group of cases the lesions causing the degeneration were remote from the lower medulla and cervical segments containing Helweg's tract. In these it could be deducted that any degenerating fibres within Helweg's tract were stray fibres from the other tract. In another group of cases the lesions were in the upper cervical cord, and so Helweg's tract was included in the lesion. In these cases no deductions could be made regarding the origin of the myelinated fibres within Helweg's tract.

In all the cases illustrated in fig. 7, the Marchi method was used, so that the degeneration shown is from well-myelinated fibres. The location of Helweg's tract is indicated by arrows. Figs. 7A and B show the location of descending fibres, degenerating after supramedullary lesions. Fig. 7A shows degeneration of the lateral vestibulospinal tract due to destruction of the vestibular nuclei by tumour, symptoms of pontine tumour first appearing five months before death. The lateral vestibulospinal tract lies peripheral to Helweg's tract in the cord, usually in relation to its anterior part. The exact relationship varies from segment to segment, as the location of the vestibulospinal tract changes. Some degenerating myelinated fibres are present within Helweg's tract. Fig. 7B shows degeneration of reticulospinal fibres in the anterior column due to necrosis of the central part of the pons resulting from thrombosis of the basilar artery, seven weeks before death. This reticulospinal tract lies deep to, and overlapping, the anterior part of Helweg's tract and it extends anteriorly and peripherally, curving round the anterior border of the tract. Some degenerating fibres are present within Helweg's tract. These and other similar cases show that some of the myelinated fibres in Helweg's tract are stray descending fibres from the lateral vestibulospinal and anterior reticulospinal tracts.

Figs. 7C–F show degeneration of the ascending spinocerebellar/spinothalamic/spinoreticular complex, due to anterolateral cordotomies in the cervical cord. The survival periods after the respective operations were 188, 150, 185 and 47 days. In figs. 7C and D, the cordotomy lesion was made in the lower cervical segments, caudal to Helweg's tract, or at least to the great majority of its fibres. In figs. 7E and F, the cordotomy lesion was made in the upper cervical segments, Helweg's tract being included in the lesion. In all these figures, it can be seen that the degenerating ascending complex lies on the periphery of the cord, posterior to Helweg's tract. It also lies deep to the tract between it and the anterior horn, and surrounds its anterior border. From previous studies (Smith, 1957) it is known that the peripheral fibres belong to the spinocerebellar system and the deeper fibres to the spinothalamic/spinoreticular complex. In all four cases, although Helweg's tract can be distinguished by its comparative pallor, there is not the clear boundary between it and

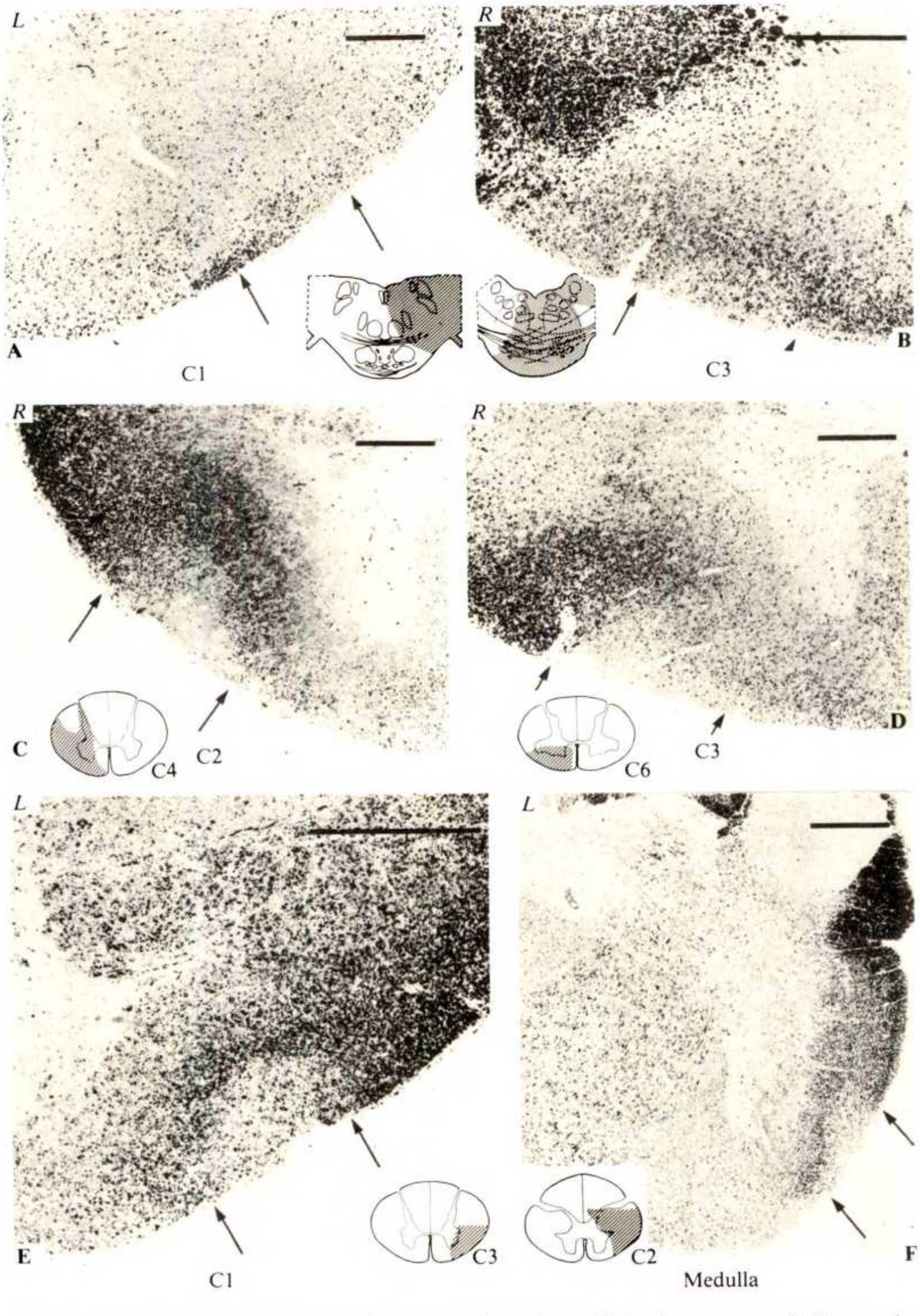

FIG. 7. A–F, relationship of various tracts, degenerating after lesions, to Helweg's tract (arrowed). Degeneration of myelinated fibres shown by black staining. A and B: descending degeneration. A, lateral vestibulospinal tract. B, pontine reticulospinal tract. C–F, ascending degeneration in anterior spinocerebellar/spinothalamic/spinoreticular complex. C and D, Helweg's tract not (or scarcely) involved in lesion. E and F, Helweg's tract involved in lesion. (Marchi preparations. A to F, bar = 1 mm.)

the ascending degenerating tracts compared to the sharp distinction between Helweg's and surrounding tracts shown in the cord in figs. 1 and 3. This is due to the presence of degenerating fibres within the tract. In figs. 7C and D, these are obviously overlapping, stray fibres from the degenerating ascending fibres. In figs. 7E and F such deductions cannot be made as Helweg's tract was included in the lesion, although it would seem most likely that they do belong to the ascending complex.

From these six cases one can draw the following conclusions regarding the relations of Helweg's tract, and the origin of the large fibres within the tract. The lateral vestibulospinal tract lies peripheral to the anterior part of Helweg's tract. The anterior reticulospinal tract lies deep to Helweg's tract, mainly its anterior part, and also lies on the periphery anterior to it. The anterior spinocerebellar tract lies on the periphery, posterior to the tract. The spinothalamic/spinoreticular complex lies deep to the spinocerebellar ttract and to Helweg's tract, surrounding Helweg's tract both medially and anteriorly. The first four cases show that stray fibres from these descending and ascending tracts run within the tract. It may be deduced from these and similar cases that many, if not all, of the larger fibres in the tract come from neighbouring tracts.

Further evidence of the different origin of the fine fibres of Helweg's tract and of the larger fibres running in it is clearly shown in the cords of patients who had motor neuron disease. In these cords there is profound degeneration of the corticospinal tracts, and frequently fibres in other tracts are also degenerated. This is illustrated in figs. 8A and B from a patient with a familial form of this disease. In this cord there is very marked degeneration throughout the anterior and lateral columns. Helweg's tracts stand out in the Marchi preparations, fig. 8A, as areas of pallor, although there is some black degeneration within them. The axons of the finer fibres have survived, as shown in fig. 8B; they are more densely packed than in the normal (*see* fig. 4C) due to the loss of the larger fibres. This and other cases of motor neuron disease provides further evidence that the larger fibres belong to other tracts, and that Helweg's tract proper consists of fine fibres.

The Polarity of the Finer Fibres in Helweg's Tract

If the origin of Helweg's tract were definitely established, the polarity of the fibres would be obvious. In the absence of this knowledge, evidence can be derived from the occurrence of degeneration after lesions of the tract. Nine cases in which the tract was transected by a high cervical cordotomy lesion provide evidence of the direction in which the fibres degenerate. In 4 of these, there was total involvement of the region of Helweg's tract. In the other 5, Helweg's tract was partially cut. In one of the cases with a partial lesion the impregnation was satisfactory only in sections cranial to the lesion, and in one other case only caudal to the lesion. In the cord shown in fig. 9, Helweg's tract was completely transected at C3, 185 days before death. The appearance of the fibres cranial to the lesion, fig. 9, C1, is normal. In fig. 9, C4, caudal to the lesion, there is loss of fine axons. In all the other cases there

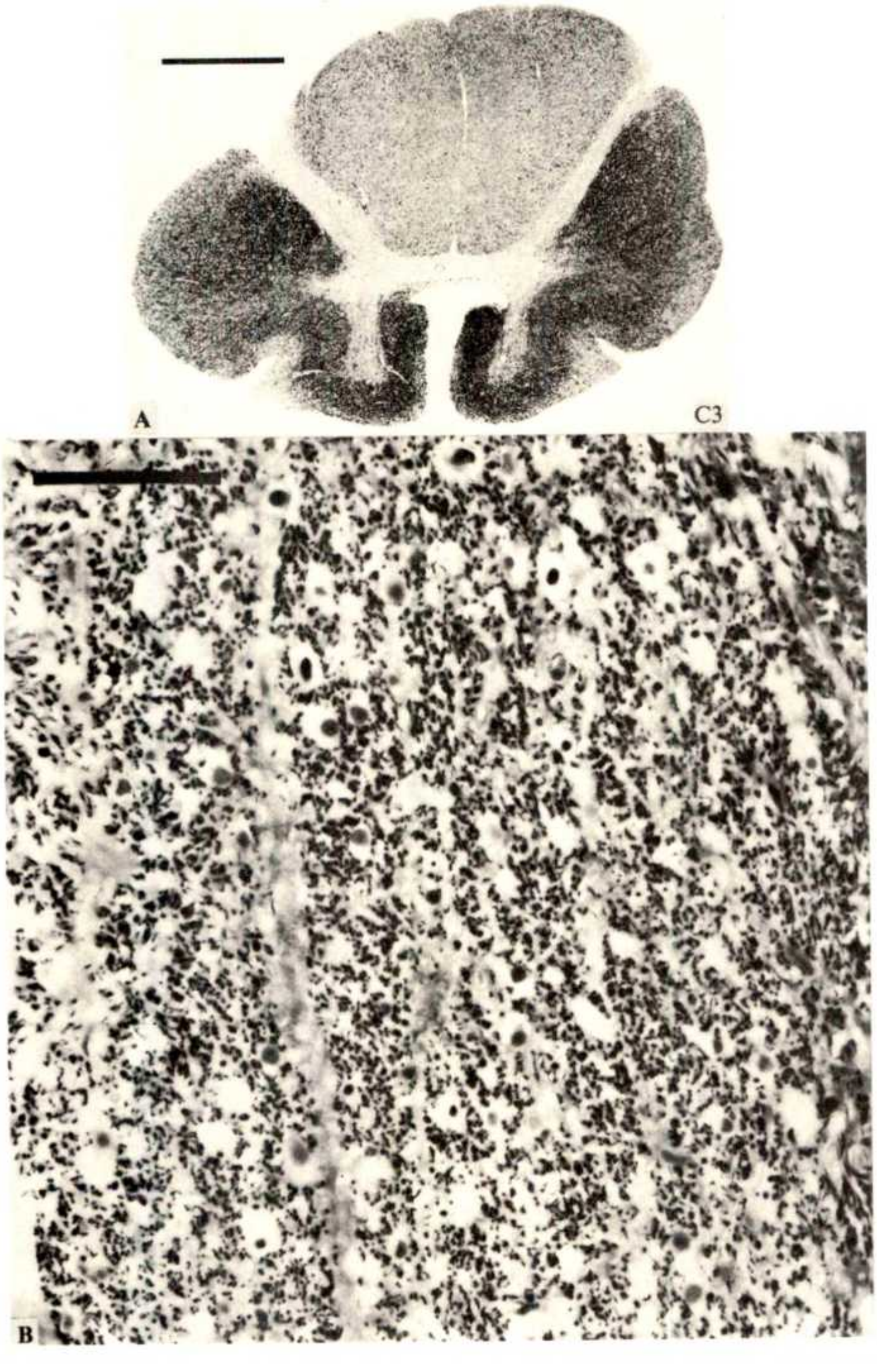

Fig. 8. Case of familial motor neuron disease. A, C3 showing profound myelin degeneration (black staining) throughout anterior and lateral columns. Helweg's tracts, although showing evidence of some myelin degeneration, stand out by their comparative pallor. (Marchi preparation. Bar = 2 mm.) B, axon preparation of Helweg's tract showing densely packed small axons (few larger myelinated fibres present—compare fig. 4C). (Marsland, Glees and Erikson: modified. Bar = 50 μm.)

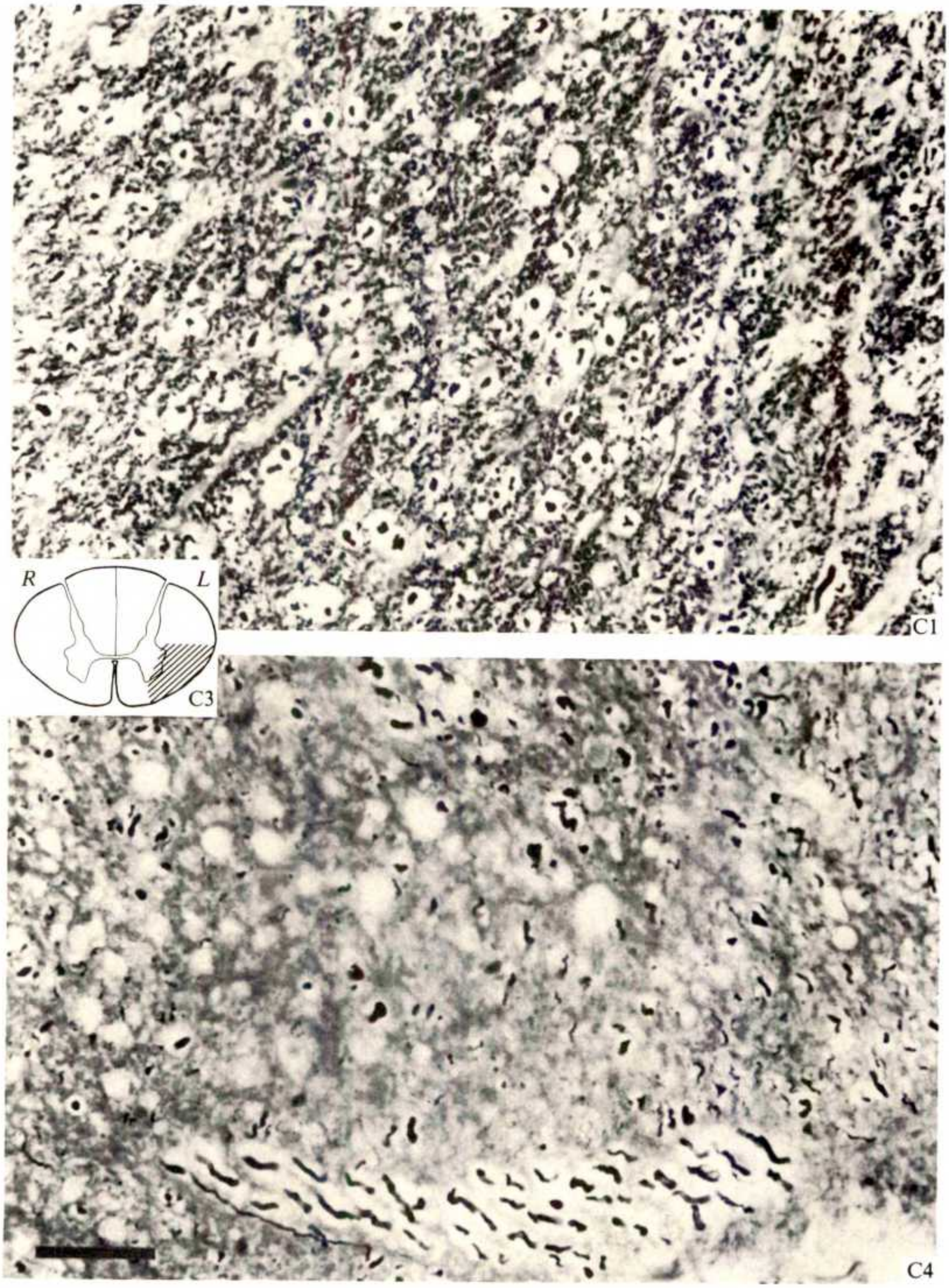

FIG. 9. Sections of Helweg's tract cranial and caudal to operative transection. C1, normal appearance of small axons, loss of some larger fibres. C4, loss of small axons, as well as of some larger fibres. Normal anterior nerve root present. (Marsland, Glees and Erikson: modified. Bar = 50 μm.)

were similar findings, fine fibres having degenerated caudal to the lesion; cranial to the lesion there were no changes in the fibres. We therefore conclude that Helweg's tract consists of fine descending fibres.

Negative Findings Regarding Origin of Helweg's Tract

We have been unable to determine the origin or termination of the fibres. We have tried to trace the fibres cranially and caudally in the normal cords, in silver preparations, but have been unable to identify the tract positively except in its peripheral location in the lower medulla and upper cervical cord.

Scattered fine fibres are present deeper in the medulla, nearer the olive, but we could not establish whether they have continuity with the tract, nor could we determine their origin nor termination. Similarly, in the cervical cord, fine fibres are present in the white matter between the periphery and the anterior horn and around the horn. The latter site is where propriospinal fibres are most abundant. We have not been able to establish whether any of these deeper fibres, described by earlier workers as 'the diffuse formation' (Okamoto, 1966) have any connection with the tract.

In all the material we have examined, the medulla and cord were cut in transverse sections. In all sections of normal cords, our impression has been that the fine fibres of the tract were cut at right angles to their long axes. We have never seen an appearance suggesting that the fibres were cut obliquely, owing to a change in their orientation. We could observe that there was a smaller number of fibres at say, C4 than in C3, but we could not identify any fibres entering or leaving the tract. In more caudal segments, we have sometimes seen very small groups or a continuous very thin layer of the fine fibres, separated from the main group, lying along the periphery of the most medial part of the anterior column and occasionally along the most anterior part of the anterior median sulcus. These fibres are cut transversely in the sections and are obviously running craniocaudally. We have not been able to trace them further.

As the olive and the central tegmental tract have been most often suggested as possible origins of Helweg's tract, we have examined 3 cases in which there were lesions of one or both of these structures. In a fourth case there was degeneration of the central tegmental tract and also concomitant degeneration of the pyramidal tract and an associated aberrant tract. In the case shown in figs. 10A–D, there was complete degeneration of the right olive and the right central tegmental tract, due to a complete left hemicerebellectomy which had been done fourteen years before death (Smith, 1975). Helweg's tract was normal on both sides of the cord. In the other 2 cases, there were lesions of the central tegmental tract. In one, a stereotactic coagulation of the spinothalamic tract in the pons was made five weeks before death. This lesion destroyed the central tegmental tract. In the other, a large necrotic lesion in the tegmentum of the upper pons, due to a head injury, destroyed the central tegmental tract. In both cases, Helweg's tract was normal. In the fourth case, fig. 11, intracerebral hæmorrhage occurred after a stereotactic operation for Parkinson's disease eight months before death (Smith, 1962). The necrosis involved most of the cerebral peduncle on the right and extended posteriorly and caudally along the lateral border of the red nucleus, involving the medial lemniscus, lateral lemniscus, anterior part of the superior cerebellar peduncle and the central tegmental tract. The results of this lesion pertinent to this paper are total degeneration of the medullary pyramid and of the central tegmental tract. (An interesting consequence of the latter is hypertrophy of the olive.) What is of special interest is the presence of an area of degeneration on the periphery of the medulla just posterior to the degenerated pyramid. This is in the region where Helweg's tract lies in the medulla (*see* fig. 1). It is also the region where Barnes (1901) described an aberrant bundle of pyramidal fibres separating from the pyramid. The occasional occurrence of this bundle has been confirmed by many other workers.

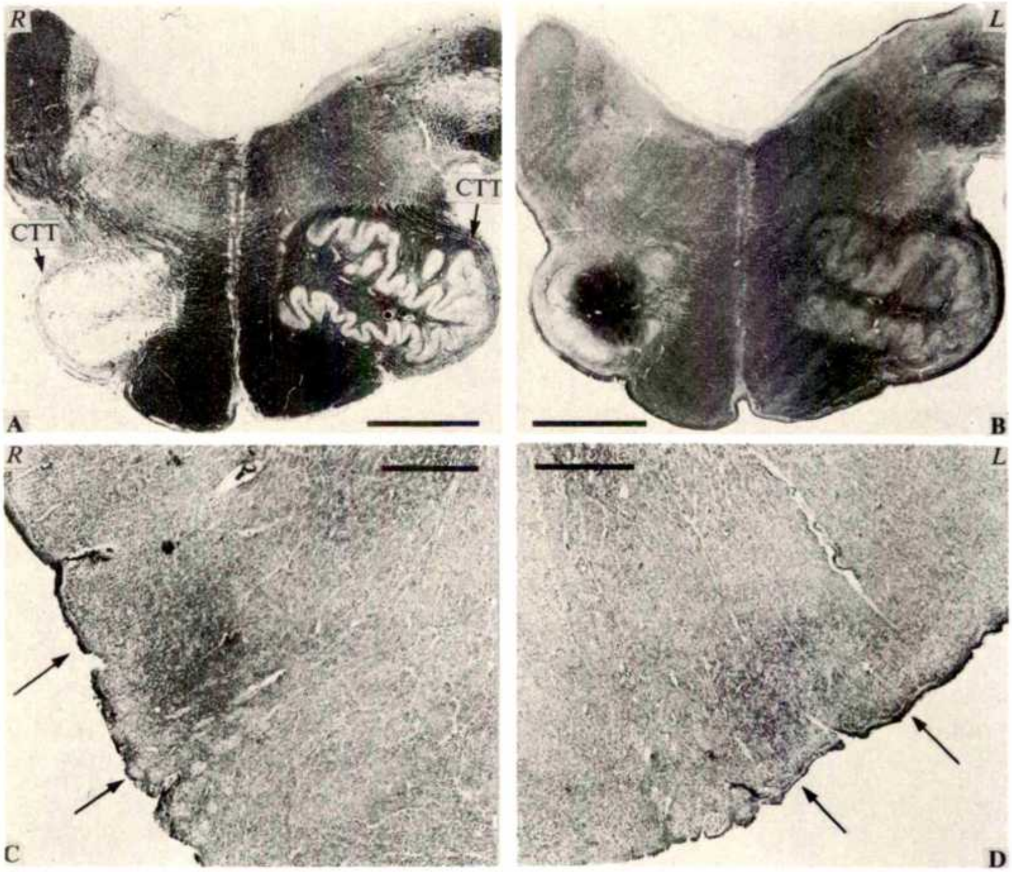

FIG. 10. Case showing retrograde degeneration of right olive and degeneration of ipsilateral central tegmental tract after left hemicerebellectomy. A, medulla. Marked shrinkage and pallor of right olive and central tegmental tract (CTT). (Loyez myelin stain. Bar = 3 mm.) B, medulla. Gliosis of right olive. (Phosphotungstic acid hæmatoxylin stain. Bar = 3 mm.) C and D, C1. Axon preparations showing normal Helweg's tracts on both sides. (Marsland, Glees and Erikson: modified. Bar = 0.5 mm.)

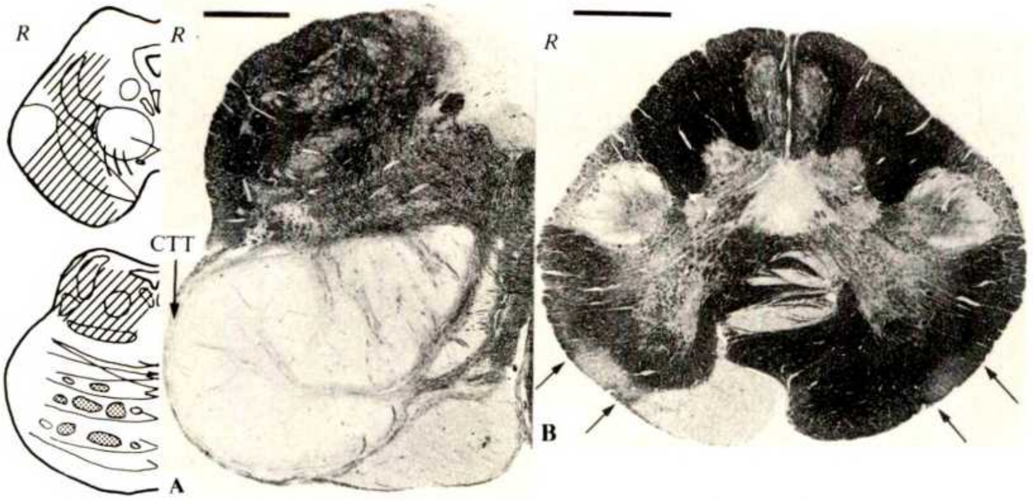

FIG. 11. Hæmorrhagic necrosis of cerebral peduncle and right tegmental region. A, mid-medulla. Marked pallor of pyramid, principal olive (also hypertrophied) and central tegmental tract (CTT). (Loyez myelin preparation. Bar = 2 mm.) B, low medulla. Marked pallor of right medullary pyramid and Helweg's tract area (arrowed). Left Helweg's tract (arrowed) recognized by slight pallor. (Loyez myelin preparation. Bar = 2 mm.)

The Japanese workers (Yamakawa, 1914; Masuda, 1963; Okamoto, 1966) consider that when Barnes' tract occurs, it displaces Helweg's tract, fibres of which may or may not be identified in Weigert Pal preparations by their pallor. We could not identify Helweg's tract on the right side of the cord in this case.

This is one of two cords in which we have not identified Helweg's tract, in sections prepared by silver impregnation methods. The tract on the contralateral side of the cord was normal. In the other cord, we could not find Helweg's tract on either side. We could not find any reason to account for its absence.

The other origin for Helweg's tract which has been suggested is the pyramidal tract. Some of the earlier workers (Russell, 1898; Collier and Buzzard, 1901, and others) considered that Helweg's tract was also degenerated when there was pyramidal tract degeneration, and the close proximity of the pyramid to Helweg's tract in the lower medulla may have seemed to support this view. We have not found any evidence of any relationship between these two tracts. In all our cases of pyramidal tract degeneration, with the single exception of the case shown in fig. 11, Helweg's tract was normal, both on the ipsilateral and contralateral side. In the case shown in fig. 12A–D there was pyramidal degeneration due to an extensive cerebral infarction eight months before death. The patient had had a unilateral cordotomy at T3, forty hours before the infarct occurred. This cordotomy had transected both anterior columns. Helweg's tract is normal on both sides. This case also provides evidence that the fine fibres of Helweg's tract do not arise from the third thoracic or more caudal segments.

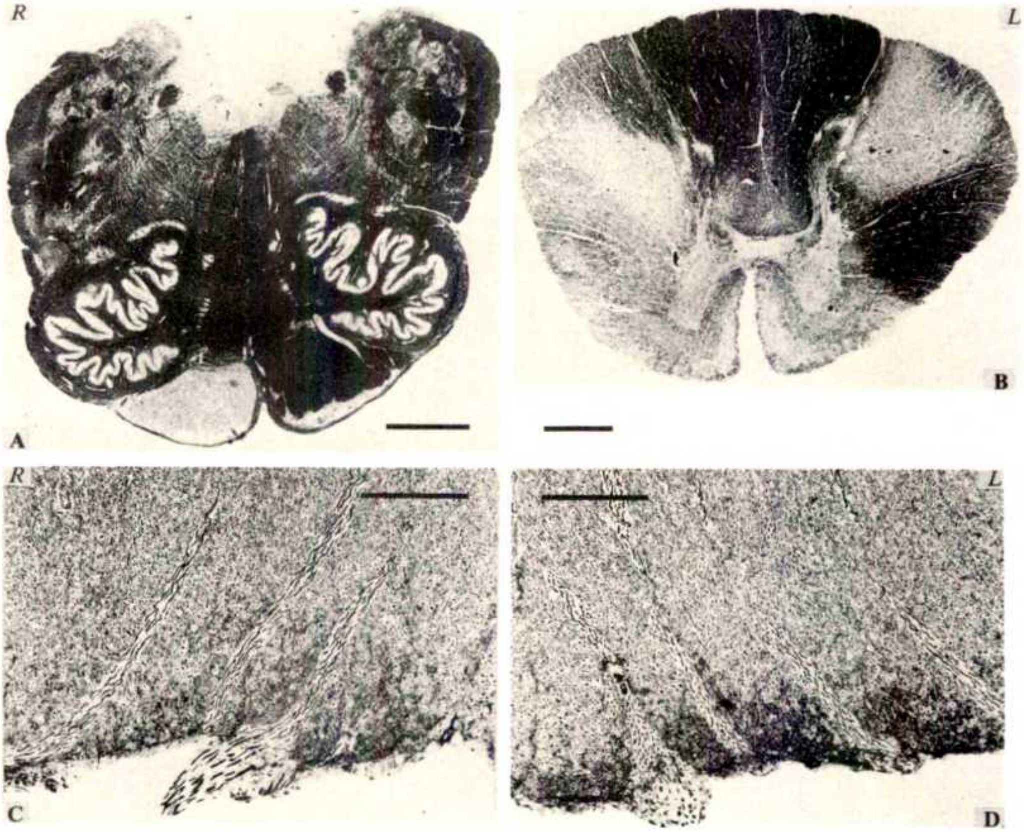

FIG. 12. A, medulla. Pyramid degenerated due to cerebral infarct. (Loyez myelin preparation. Bar = 3 mm.) B, T3. Transection of both anterior columns and most of right lateral column in cordotomy lesion. (Loyez myelin preparation. Bar = 1 mm.) C and D, C4. Normal Helweg's tract on both sides. (Marsland, Glees and Erikson: modified. Bar = 0.3 mm.)

DISCUSSION

Although the location of Helweg's tract is commonly included in textbook diagrams of the human cervical cord, it is seldom mentioned today by neuropathologists or neuroanatomists. A probable reason for this is that the clear delineation of the tract in Weigert Pal preparations, formerly the most frequent myelin stain used on human material, is rarely equalled in other myelin preparations. In fact, the normal appearance of pallor in the tract in Weigert Pal preparations is that which, in other sites, would be interpreted as indicating degeneration, as has been shown here. In other myelin preparations, Helweg's tract may be seen as a vaguely paler area, though this can easily be missed.

The characteristic feature of Helweg's tract is the very high proportion of fine nerve fibres in it. The earliest observers of the tract noted that the fibres were among the finest in the spinal cord (Helweg, 1888; von Bechterew, 1894); the methods available at the time did not permit any detailed study of their calibre. Okamoto (1966) reported, from Weigert Pal material, that the dominant fibres measured less than 1 μm in diameter. He observed that some of the fibres were well stained by the Weigert Pal method, although the majority remained unstained.

The present study has confirmed that the most striking feature of the tract is the very large number of fine fibres in it. It has also shown that almost all these fibres are myelinated, even those as small as 0.37 μm. In more than two-thirds of the fine fibres the myelin sheath is thin or very thin; in many of them the total diameter of the fibre is only minimally larger than that of the axon. This applies even to fibres up to 2.5 μm in diameter. In rather less than one-third of the fine fibres the appearance is different. These fibres have a thick myelin sheath, in some the total diameter being almost three times that of the axon.

We have found that the g ratio (*see* p. 256) in all the fine fibres varies between 0.29 and 0.89, irrespective of the total diameter of the fibre. This does not fit in with the observations of Hildebrand and Hahn (1978) on the relation of myelin sheath thickness and axon size in the spinal cord of various species, the cat being the highest mammal studied. They reported that the sheaths of myelinated nerve fibres increase in thickness with the size of the axons, in the central as well as the peripheral nervous system. They found that this increase followed a fairly straight line below an axon size of 4.5 μm. As very few ultramicroscopic studies have been made on the central nervous system, we do not know if the variation that we have found in Helweg's tract also occurs in other tracts in man.

The origin of the larger myelinated fibres in the tract will be considered first. These fibres stand out as being so different from the dominant fine fibres that it has always been thought they are not part of Helweg's tract proper, and that it is most likely that they are stray fibres from other tracts (von Bechterew, 1901; Obersteiner, 1901). Okamoto (1966) concluded from myelogenetic studies that these were all descending fibres, of reticulospinal, tectospinal and vestibulospinal origin, basing his conclusions on the coincidence of the time of myelination of fibres in neighbouring and Helweg's tracts. He did not find that any of the fibres were anterior spinocerebellar or spinothalamic. Our study of degenerating fibres within the territory of Helweg's tract has confirmed that some of the larger fibres within the tract are vestibulospinal and reticulospinal. We have no evidence regarding the tectospinal tract. We have shown that spinocerebellar fibres and fibres from the spinothalamic/spinoreticular complex run within Helweg's tract. One cannot positively state that all the larger myelinated fibres within Helweg's tract are stray fibres from other tracts, but this seems likely, as all these tracts are adjacent to Helweg's tract in the spinal cord. Two further observations support the view that the larger myelinated fibres are from other tracts. One is the fact that there are fewer large fibres in Helweg's tract in the medulla than in the cord. In the medulla, Helweg's tract has a close relationship only with the anterolateral ascending fibre complex. The vestibulospinal and reticulospinal tracts do not run near Helweg's tract until they enter the cord. Therefore, there are fewer stray fibres in Helweg's tract in the medulla. The other observation comes from the cases of motor neuron disease. In the cords of the patients who had very profound degeneration in the anterior and lateral columns, the larger myelinated fibres in Helweg's tract were degenerated whereas the finer fibres survived.

It is tempting to postulate that all the well-myelinated fibres measuring more than 2.5 μm do not belong to Helweg's tract proper. But it is not possible to state this definitely, nor to define the limits of the calibre of fibres specific to Helweg's tract, until further calibre spectrum data of the neighbouring tracts is obtained.

We will now consider the polarity of the fibres in Helweg's tract. Previous ideas as to the polarity of the fibres have been largely conjectural, as the origin and termination of the tract is not known. The tract has been thought to be either descending or ascending, depending either on its postulated origin, or on the degeneration of the larger myelinated fibres. These are now recognized as belonging to other tracts. The views of earlier workers are well reviewed by Okamoto (1966) and will not be repeated here. Okamoto and his colleagues (Okamoto, 1966; Mizuno *et al.*, 1968) considered that the tract was ascending.

We have presented evidence here that this is a descending tract, based on nine cases showing degeneration of the fine axons in Helweg's tract, after lesions of the tract itself. Such a study has not been reported previously. In all the cases we have found that the fine fibres in the tract degenerate caudal to transection, and that the fine fibres cranial to the tract are intact. We have therefore concluded that the fine fibres of the tract are descending.

It is necessary to add a comment on our evidence. This is based on cases in which the tract was divided, wholly or partially, in the second or third cervical segment, and our conclusions therefore apply only to fibres already present in the tract at these levels. We cannot take it as definitely proven that the tract cranial to C2 contains absolutely no ascending fibres. Proof of this would depend on the examination of the tract after a lesion destroying it in the medulla. But, in view of the unique character of its constituent fine fibres, it would seem most likely that these all belong to the same system and that Helweg's is entirely a descending tract.

We now wish to consider the various structures which have most frequently been suggested as giving origin to the tract: the olive, the central tegmental tract, the pyramidal tract and cells of the anterior horn. The olive has most often been thought to have an association with the tract. It has its maximum size at the level of the lower pole of the olive, and disappears abruptly cranial to this level, as was noted by von Bechterew (1894). He called the tract '*olivenstrang*', but found no proof of a direct relationship between its fibres and neurons of the olive. No subsequent paper has positively established any relationship between them, although a number of authors suggested that the tract originated in the olive (Pick, 1898; Thalbitzer, 1910; Anton and Zingerle, 1914). Sie (1956) observed the loss of fine fibres in Helweg's tract caudal to brain-stem lesions in two cases. He attributed this fibre loss to partial lesions of the olive, but had no justification for this assumption; for in one case there were extensive softenings from the mesencephalon almost to the cord, and in the other case, thrombosis of a branch of the posterior cerebellar artery had caused destruction of much of the left tegmentum of the medulla. Okamoto (1966) found the tract to be normal in a case of olivocerebellar degeneration, studied in Weigert Pal preparations. And with his colleagues (Mizuno *et al.*, 1968) he reported that the tract was present in two anencephalic fœtuses in which the olive was not developed. We have also found that the tract was normal in a case in which there was almost total degeneration of the olive. On the evidence from the literature and from our own material, it can be concluded that Helweg's tract does not arise from the olive.

With regard to the suggestion that the tract is a caudal extension of the central tegmental tract, we have provided evidence that the tract was normal in three cases in which the central tegmental tract was degenerated. In one of these cases, the olive was also degenerated. In the other two, the central tegmental tract had been destroyed in brain-stem lesions. It can therefore be concluded that Helweg's tract is not part of the central tegmental tract.

The other most commonly suggested origin for Helweg's tract is the pyramidal tract. We have found no basis for this view as the tract was normal in all cases, except one, in which there was degeneration of the pyramidal tract, due either to cerebral or brain-stem lesions or to motor neuron disease. The exception will be discussed later.

Another postulated origin of the tract are the cells of the anterior horns (von Bechterew, 1899; Mizuno, Yoshida and Okamoto, 1968). The latter based their views on the study of nine anencephalic fœtuses. In two of these, Helweg's tract was identified. In these fœtuses the anterior horns and lower brain-stem were better developed than the fœtuses in whom the tract was absent. It was therefore thought that the tract consists, mainly at least, of ascending fibres, especially spinoreticular. In this study no continuity between any cells and Helweg's tract was in fact established. The deduction could, therefore, equally well be made that the tract was descending, for example, reticulospinal.

The possibility that the fibres of Helweg's tract are solely or entirely spino-olivary will now be considered. Brodal *et al* (1950) described spino-olivary fibres in the cat, and on this basis suggested that the fibres of Helweg's tract in man were probably spino-olivary and that olivospinal fibres were presumably not present. There are marked dissimilarities between the spino-olivary projection in the cat, arising mainly from lumbosacral segments and projecting to the medial and dorsal accessory olives, and a tract existing only in the upper cervical segments and lower medulla in man. Nevertheless, current textbooks of human anatomy have perpetuated the concept that Helweg's tract consists solely (Carpenter, 1976) or partly (Williams and Warwick, 1975) of spino-olivary fibres. The existence of spino-olivary fibres in cat and monkey has been confirmed (Mehler, Feferman and Nauta, 1960; Kerr, 1975). But the evidence for the presence of any spino-olivary fibres in any part of the anterior column of man, not specifically in Helweg's tract, indicates that they are very few. Bowsher (1962) reported his findings on the projection of fibres from the anterolateral quadrant of man, in the lower brain-stem. This study was based on degeneration of the preterminal part of axons, destroyed in the anterolateral quadrant of the human spinal cord in the operation of anterolateral cordotomy. There were 8 lesions in 7 cases. He described preterminal degeneration in the olive in 4 out of 7 cases (8 cordotomies) 'only a small amount of degeneration of very fine fibres was seen in the caudal part of the principal olive'. Mehler (1962) made a very detailed study of the distribution of degenerating ascending fibres after a bilateral cordotomy in man. He did not mention any degeneration in the olive, nor show any in his diagrams. And in his extensive experimental study of comparable axon degeneration in the monkey (Mehler *et al.*, 1960) he writes, with reference to the termination of fibres in paleo-olivary structures, 'It should be pointed out, however, that premature application of these findings to man should be avoided. While comparable spino-olivary connexions have been observed in several species of monkeys, as well as a representative series of sub-primate species, we have been unable to demonstrate satisfactorily homologous connexions in either the chimpanzee or man following complete anterolateral cordotomy.'

In our own extensive material from patients who had had anterolateral cordotomies, in which ascending degeneration was traced, mainly by the Marchi method, we have found only a very occasional degenerating fibre in the region of the olive. In anticipation of possible criticisms of the limitations of the Marchi method, we must stress that findings were negative, even after high cervical lesions in which the degeneration elsewhere in the medulla, shown by this method, was very profuse. Further, we have not found any evidence of degeneration in the fine fibres of Helweg's tract after anterolateral cordotomies caudal to the tract.

The evidence from the literature and our own material is therefore that spino-olivary fibres in any part of the anterior quadrant of the human cord are few. There is, in particular, no evidence that any spino-olivary fibres run in Helweg's tract. The extrapolation of findings from experimental material, even primate, to man, cannot be justified without adequate confirmation of comparable findings in man.

The introduction of the term 'olive' into the name commonly used for Helweg's tract was most unfortunate. Von Bechterew (1894) in calling the tract the *Olivenstrang* did not imply a definite relationship with the olive, but the use of the term, together with the anatomical proximity of the olive and the upper part of the tract, has led to the general impression that there is a connection between them, and the tract has been described, without anatomical foundation, as olivospinal or spino-olivary, for almost ninety years. The evidence from the literature, as well as the new evidence presented here, shows that there is no basis at all at present for considering the tract to be olivospinal nor any basis for considering it to be spino-olivary. In view of the absence of evidence of a connection between Helweg's tract and the olive, either efferent or afferent, we consider that the use of the erroneous and misleading terms 'olivospinal tract' and 'spino-olivary tract' in human anatomy should be discontinued. Until such time as the origin of the tract is established, the use of the eponymous title or the term 'triangular tract' is recommended.

We now want to consider the anatomical relationship between Helweg's and other tracts. In current textbook diagrams, Helweg's tract, labelled either as olivospinal tract and spino-olivary tract (Crosby, Humphrey and Lauer, 1962) or spino-olivary (Carpenter, 1976) is shown on the periphery of the cord, anterior to the anterior spinocerebellar tract and posterior to, and separate from, the lateral vestibulospinal and reticulospinal tracts. We have shown that Helweg's tract has a very close relationship with these ascending and descending tracts as well as with the spinothalamic/spinoreticular complex. The lateral vestibulospinal tract lies, at least in part, peripheral to the anterior part of Helweg's tract. This was shown also by Sie (1956). Reticulospinal fibres overlap the medial aspects of the anterior part of the tract and also lie anterior to its anterior border. The anterior spinocerebellar tract lies on the periphery of the cord posterior to Helweg's tract. The posterior fibres of the spinothalamic/spinoreticular complex lie medial to the anterior spinocerebellar tract and the anterior fibres of this complex lie medial to Helweg's tract, and surround its anterior border. These anterior fibres are from the most cranial segments of the cord. Where Helweg's tract is large, from the third cervical segment to the lower medulla, the impression is that the mass of tightly-packed fibres of the tract force the ascending fibres into a more medial location. This may be of relevance to the depth of incision necessary to divide these ascending fibres in cervical anterolateral cordotomies.

The last tract we want to mention in relation to Helweg's tract is the anterolateral pyramidal tract first described by Barnes (1901). This is an aberrant compact group of fibres which separates off from the corticospinal tract in the lower pons or the medulla, to lie more posteriorly on the periphery of the medulla, and to descend ipsilaterally into the upper cervical cord. The aberrant tract occupies, in the lower medulla and spinal cord, the same location as Helweg's tract (Yamakawa, 1914, and Mizuno *et al.*, 1968). Mizuno, Nakamura and Okamoto (1968) studied the frequency of occurrence of Barnes' tract in 210 Japanese, finding it in 43 out of 210 cases, bilaterally in 16, unilaterally in 27. Barnes' tract can be distinguished from Helweg's by its normal dark staining in myelin preparations. Helweg's tract can be distinguished by its pallor. It is usually displaced medially by the aberrant tract, but in some cases cannot be identified (Mizuno, Nakamura and Okamoto, 1968). We have found only one instance of what appears to be a Barnes' tract. In this case, in which brain-stem necrosis had involved both the cerebral peduncle and the central tegmental tract, the medullary pyramid was completely degenerated. Helweg's tract area on the same side, in myelin preparations, was much paler than the contralateral Helweg's tract. We could not find any evidence of the fine fibres of Helweg's tract, in axon preparations, on the side of the degenerated pyramid, neither in the medulla nor in the spinal cord. We therefore consider that in this case a Barnes' anterolateral pyramidal tract had displaced Helweg's tract. This is the only case in which we could not find any evidence of Helweg's tract on one side of the cord, but in which we found evidence of Barnes' tract in the same cord, out of the large number of cords examined, so it would appear likely that Barnes' tract may occur less frequently in

Western races than in the Japanese. In the only other cord in which we could not find Helweg's tract on either side, we could not find evidence of aberrant corticospinal fibres in the area of the tract.

Decisions regarding the function of Helweg's tract must obviously wait for knowledge of its origin and termination, but certain features of the tract are worth considering. The evidence shows that this is a descending tract, starting in the medulla and descending in the cervical cord to the fifth segment and occasionally further caudally. The tract is largest in its medullary part. The fibres are very fine. The majority of these fibres are very thinly myelinated, a smaller number of the fine fibres are thickly myelinated. It is possible that these two types of fibre have different origins and function. The dominance of the very thinly myelinated fibres indicate that the tract must be mainly a slowly conducting tract.

Helweg's tract is unique in the cord, not only because of the fineness of its fibres and the poverty of myelin which characterizes it, but also because of its location on the periphery of the cord. Elsewhere, this location is occupied by long tracts, the majority ascending. Why should such a short tract occupy this position? The fine fibre structure of the tract and its relation to the exit of the anterior nerve roots crossing it led to the suggestion that the tract represented a centrifugal vasomotor path (Reinhold, 1897). There is no evidence, however, to support this, although Thalbitzer (1910) considered that the fibres ran into the anterior roots. This is a novel but tempting anatomical concept, which would account for the disappearance of the fibres from the periphery of the cord, but we have not been able to confirm it.

In any speculation regarding the nature of the tract, the possibility that it is a reticulospinal pathway must be considered. In this connection, we should like to draw attention to the difference between the fine, very thinly myelinated fibres of the tract, and the character of fibres of other reticulospinal tracts. We have found several groups of reticulospinal fibres of medullary origin. These are well myelinated and contain many large fibres. The pontine reticulospinal tract is also well myelinated, although its fibres are finer. This does not imply that Helweg's tract could not be a reticulospinal tract, but suggests that, if it is, its cells of origin must be of a different type from those of other reticulospinal fibres.

SUMMARY

It has been confirmed that Helweg's tract is a constant component of the lower medulla and cervical cord in man. It is present, on the periphery, in the first five cervical segments and occasionally more caudally; it has its maximum size in the medulla and upper three segments; in the second and third segment it has its characteristic triangular shape.

The tract has been studied in axon preparations and shown to be easily identified by its very dark appearance. The fibre spectrum in the tract is compared with that of other tracts. The tract was also studied in semi-thin and ultra-thin sections. The most striking characteristics of the tract are the very large number of very fine fibres,

and the fact that almost all these fibres are myelinated. In about two-thirds of these fine fibres the myelin sheath is thin or very thin, in the other third the myelin sheath is thick. Non-myelinated fibres are very few. Larger myelinated fibres are also present, but most of them do not belong to Helweg's tract. Preliminary measurements of the calibre of the various fibres and an estimation of their proportional representation have been made.

The polarity of the fine fibres has been studied and it is shown that the majority, and probably all, of these fibres are descending.

The fine fibres have been shown to have no relationship with the olive, neither efferent nor afferent. It has also been shown that the fine fibres do not take origin from the central tegmental tract or the pyramidal tract.

The anatomical relationship of Helweg's tract to neighbouring tracts has been demonstrated. These tracts are the source of most, if not all, of the larger fibres in Helweg's tract.

The significance of the close relationship of Helweg's tract to the spinothalamic/spinoreticular complex has been discussed in respect to cervical cordotomy operations.

The tract is clearly seen in Weigert Pal preparations, where it stands out because of its marked pallor. This pallor has been shown to have the same appearance as that indicating degeneration in other tracts and possible errors in the interpretation of sections are illustrated.

The origin and termination of the tract have not been determined. Previous observations by other workers that Helweg's tract is displaced or absent in cases in which there is an aberrant anterolateral corticospinal tract, Barnes' bundle, is confirmed.

ACKNOWLEDGEMENTS

We are most grateful to Dr David Landon and his staff for all their help. The preparation and examination of the semi-thin and ultra-thin sections by Dr Landon is a most important part of the study reported here.

We also want to express our great indebtedness to Miss Ursula Starega and Mr William Bessant. Miss Starega has developed and perfected the modification of the Marsland, Glees and Erikson silver impregnation method, which has formed the main basis for our observations and conclusions. Mr Bessant has shown the greatest skill and patience in making an excellent photographic record of all the material.

We also want to thank all the clinicians and pathologists who have so generously given us the cases studied.

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(*Received July 15, 1980*)

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ALTERATIONS IN THE NUMBER AND AFFINITY OF JUNCTIONAL ACETYLCHOLINE RECEPTORS IN A MYOPATHY WITH TUBULAR AGGREGATES

A NEWLY RECOGNIZED RECEPTOR DEFECT

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INTRODUCTION

WALTON AND NATTRASS (1954) originally applied the term 'myasthenic myopathy' to certain rare clinical syndromes characterized by weakness and muscular fatiguability that often showed a favourable response to anticholinesterase drugs. The nature of the defect in these cases was not clearly defined, but limited electromyographic and muscle biopsy studies pointed to an underlying myopathy (Rowland and Eskanazi, 1956; Walton, Geschwind and Simpson, 1956; Rowland, Lisak, Schotland, De Jesus and Berg, 1973). Subsequent observations on several patients with this type of syndrome revealed a defect in neuromuscular transmission which was similar to that observed in myasthenia gravis. McQuillen (1966) demonstrated these changes in two siblings with neostigmine-responsive limb girdle weakness and his findings have been confirmed in other cases (Johns, Campa and Adelman, 1973; Dobkin and Verity, 1978). Although muscle biopsies were reported to be normal in McQuillen's cases, studies using histochemical and ultrastructural techniques have sometimes revealed striking and distinctive changes, characterized by the presence of tubular aggregates (Johns *et al.*, 1973; Dobkin and Verity, 1978; Engel, Lambert, Mulder, Torres, Sahashi, Bertorini and Whitaker, 1979).

In this paper we report the findings in a 32-year-old man with tubular aggregates on muscle biopsy who presented in adult life with intermittent diplopia, mild non-progressive dysphagia and variable weakness of the limbs and trunk. Investigations of neuromuscular transmission showed a small decremental response, increased jitter and blocking of some components. Studies of junctional acetylcholine receptors (AChR) using ^{125}I-labelled α-bungarotoxin showed a greatly reduced number of receptors similar to that seen in myasthenia gravis (Fambrough, Drachman and Satyamurti, 1973; Ito, Miledi, Vincent and Newsom-Davis, 1978). Unlike the findings in myasthenia gravis, however, the patient's receptors showed marked changes in the affinity of binding for the non-depolarizing antagonist d-tubocurarine. These results taken in conjunction with the clinical, morphological and electron microscopic findings suggest that the patient is suffering from a newly recognized and pathogenetically distinct type of receptor defect.

CASE HISTORY

A.A., a 32-year-old Iranian man, was first seen at the National Hospital in 1976 with a fourteen-month history of mild non-progressive dysphagia and a ten-month history of intermittent diplopia and fluctuating weakness in the limbs. His parents were first cousins. Two brothers and three sisters were said to be unaffected but two younger siblings died in infancy of unknown causes.

His birth and early development were normal. He was able to run and play games at school but had some difficulty in keeping up with his peers and usually came last in competitive races. In June, 1975 he first noticed slight difficulty with swallowing. This symptom remained constant throughout the day and was not worse at the end of a meal. In October, 1974 he had three episodes of double vision, lasting three days, two days and six hours, respectively, which had not recurred. At the same time, he began to notice weakness and tiredness in the limbs associated with difficulty in getting out of a low chair, climbing stairs and lifting his arms above his head. There was no diurnal variation in the severity of symptoms but at times the weakness was more marked. These episodes of increased weakness usually lasted several days and were not directly related to undue physical exertion.

In November, 1975 he was investigated in Tehran where an edrophonium test was negative and a left triceps muscle biopsy was said to be normal. He was given a trial of prednisone 60 mg daily with subjective improvement in muscle strength, although the dysphagia remained unchanged. After three weeks the dose of prednisone was gradually tapered to a maintenance level of 10 mg a day without further benefit.

When first seen at the National Hospital in August, 1976 the patient was taking 10 mg of prednisone daily. There was fatiguable ptosis of the left eyelid, and diplopia without observable extraocular weakness developed during sustained elevation of the eyes. The facial muscles were weak bilaterally and his speech had a nasal quality. Neck flexion was minimally weak. His gait was normal but he had difficulty in climbing a steep step and was unable to sit up from a supine position without using his arms. The limb muscles were generally thin but there was no focal wasting. There was mild diffuse weakness (4/5 on the MRC scale) which affected all muscle groups but was more marked proximally. Muscle power diminished slightly on sustained contraction against resistance but fatigue was not a prominent clinical finding. He was able to maintain his leg raised off the bed for forty-five seconds. Deep tendon reflexes were normal and there was no sensory loss. General physical examination was also normal with a blood pressure of 120/70.

After various investigations, including EMG and muscle biopsy (*see below*), the prednisone dosage was increased to 30 mg on alternate days with considerable improvement in muscle strength. Within three weeks the patient was able to step up a steep step and rise from a supine position without using his arms. His speech returned to normal, but mild dysphagia persisted. He returned to Tehran in October 1976 and was maintained on alternate-day prednisone (25 to 30 mg) until the beginning of 1979, when the dose was gradually reduced and finally stopped in May of that year. Improvement had been maintained throughout the period of treatment but symptoms returned soon after the prednisone was withdrawn.

When seen again in July, 1979 the findings were similar to those recorded in 1976. They consisted of fatiguable left-sided ptosis, weakness of the face, soft palate and neck flexors, and mild diffuse weakness in the limbs and trunk with difficulty in climbing steep steps and in rising from a supine position. An edrophonium test showed slight improvement in the truncal muscles enabling him to sit up from a supine position unaided, but speech and limb muscles were unaltered. Following further investigations, including an intercostal muscle biopsy (*see below*), the patient was again started on prednisone in a dose of 25 mg on alternate days. Within one month there had been a considerable improvement in muscle strength and his speech had returned to normal. Mild dysphagia persisted. He returned to Tehran on alternate-day prednisone and potassium supplements.

ROUTINE INVESTIGATIONS

The following laboratory investigations were normal in 1976 and again in 1979: hæmoglobin, full blood count, sedimentation rate, WR, blood sugar, T4, plasma sodium, potassium and chloride, blood urea, serum calcium, inorganic phosphorous, alkaline phosphatase and creatine phosphokinase. An autoantibody screen was negative except for the presence of weakly positive gastric parietal cell antibodies. Acetylcholine receptor antibodies were not detected. An ECG, chest x-ray, tomograms and a CAT scan of the anterior mediastinum were normal.

Electromyographic sampling of the right deltoid and biceps muscles with a concentric needle electrode showed myopathic changes with many polyphasic motor unit action potentials of short duration and small amplitude. There was a full interference pattern of maximal amplitude around 2 mV with weak effort which gradually diminished during sustained contraction. Motor conduction velocity in the right median nerve was 70 m. s^{-1} with a distal latency of 3.5 ms.

Tests of Neuromuscular Transmission

A Medelec MS6 electromyograph was used in these studies. Short trains of stimuli at 3 Hz and 5 Hz were delivered to the right ulnar nerve at the wrist. Muscle action potentials were recorded from the abductor digiti minimi through surface electrodes placed over the muscle belly and over the tendon. Single fibre electromyography was performed on the extensor digitorum communis muscle using a Medelec SF25 needle, according to methods described by Stålberg, Ekstedt and Broman (1974).

With repetitive superamaximal nerve stimulation there was a small decrement in the amplitude of the evoked muscle action potential which measured 15 per cent at 3 Hz and 14 per cent at 5 Hz. This decrement was absent when a further train of stimuli was delivered to the nerve immediately after fifteen seconds of maximal voluntary contraction but four minutes later had increased to 18 per cent. With single fibre electromyography in the extensor digitorum communis muscle, many potential pairs showed increased jitter and some showed intermittent blocking of components (fig. 1).

SPECIAL INVESTIGATIONS

Muscle Biopsy

Samples were obtained from the right triceps muscle (August, 1976) and from the left ninth external intercostal muscle (September, 1979) under local anæsthesia. Specimens from the right triceps muscle were processed for histochemistry and electron microscopy as described previously (Morgan-Hughes, Mair and Lascelles, 1970). The intercostal biopsy was used for histochemistry, electron microscopy and

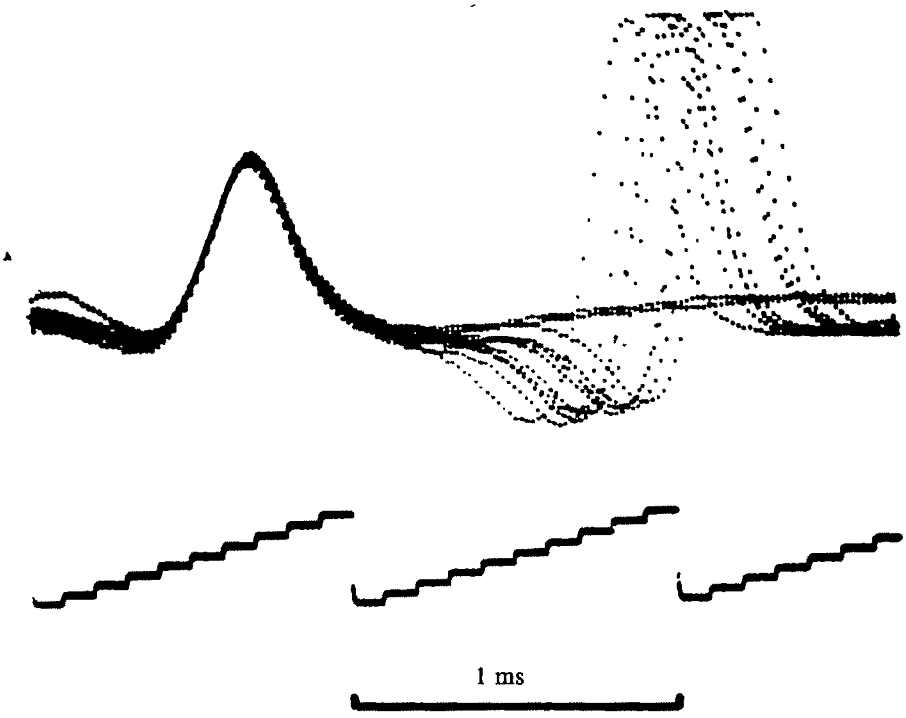

FIG. 1. Single fibre recording from extensor digitorum communis to show increased jitter and intermittent blocking of some components.

for studying junctional acetylcholine receptors. Teased muscle fibres from the intercostal muscle biopsy were stained by the Karnovsky-Roots (1964) method to demonstrate acetylcholine esterase activity.

Studies of Acetylcholine Receptors (AChR)

Details of the methods, preparation of the labelled toxin and the analysis of binding data are given elsewhere (Darveniza, Morgan-Hughes and Thompson, 1979; Darveniza, 1980). A sample of freshly isolated intercostal muscle was carefully teased into small bundles of 5 to 15 fibres under the dissecting microscope. The teasing medium consisted of 50 per cent glycerol (V/V) in buffered Hartmann's solution to which 5 mg/ml of bovine serum albumin had been added (final pH 7.3). After washing, fibres were incubated in 50 nmol/l di-iodinated ^{125}I-α-bungarotoxin (SA of 201 Ci/mmol) at 22° C for different times, washed, fixed in 2.5 per cent buffered glutaraldehyde and stained by the Karnovsky-Roots method to identify end-plates. They were then cut into end-plate and non-end-plate segments of similar length ($\simeq$ 200 μm). Equal numbers of end-plate and non-end-plate segments (65 to 110) for each incubation time were counted separately in an LKB Wallac 80,000 gamma counter. Specific binding to junctional AChR was taken to be the difference between the end-plate (total) and the non-end-plate (non-specific) gamma counts and expressed as attomoles bound per end-plate. The association rate constant (k_{+1}) was calculated from a semi-logarithmic plot of the fraction of unoccupied binding sites against time. The number of ^{125}I-α-bgtx binding sites per end-plate was assumed to be equivalent to the number of AChR (*see* Heidmann and Changeux, 1978; Darveniza, 1980).

Specific binding of the non-depolarizing antagonist d-tubocurarine was also studied by examining its effect at equilibrium on the rate of toxin binding. Fibres were equilibrated with different concentrations of the ligand and then incubated short of saturation (20 min) in 50 nmol/l ^{125}I-α-bgtx containing the same concentrations of tubocurarine. The data is expressed in the form of a logarithmic plot (formally similar to a Hill plot) of $(r-1)$ against [I] where r is the ratio of the first order rate constant (k) for toxin binding in the absence of ligand to the observed rate constant (K_{obs}) in its presence (k/k_{obs}) and [I] is the ligand concentration.

The I_{50} value for tubocurarine (that concentration of tubocurarine which halves the rate of toxin binding) which is a measure of its affinity for AChR was determined from the equation: $(r-1) = [I/I_{50}]^h$ where h is the Hill coefficient. Thus with 50 per cent inhibition in the rate of toxin binding, i.e. when $(r-1) = 1$ then $I = I_{50}$ (after Colquhoun and Rang, 1976).

In all experiments specific binding of ^{125}I-α-bgtx exceeded non-specific binding at least threefold except where a high degree of inhibition occurred as with 100 umol/l tubocurarine. The results are compared with similar data from 16 patients with myasthenia gravis and 16 'control' subjects without neuromuscular disease who underwent chest surgery for other reasons (Lecky and Morgan-Hughes, 1981).

RESULTS

Muscle Histochemistry

Right triceps. In sections stained with the modified Gomori trichrome method, a high proportion of the fibres in some fascicles contained large, irregular bright red deposits which usually extended from beneath the plasma membrane into the central regions. These deposits, which occupied a considerable part of the total cross sectional area of the fibres, exhibited the typical cytochemical characteristics of tubular aggregates. They showed an intense reaction for NADH tetrazolium reductase (fig. 2) but were unstained by reactions for succinic dehydrogenase and α-glycerophosphate dehydrogenase. They lacked myofibrillar material (fig. 3), were confined to the histochemical type 2 fibres and contained increased amounts of PAS-positive material. Fibres with tubular aggregates were largely confined to certain fascicles leaving others relatively unaffected (fig. 2). In affected fascicles, nearly all the type 2 fibres were involved. The biopsy contained 88 per cent type 2 fibres and only 12 per cent were type 1. Diameters ranged from 45 to 80 μm for the type 1 fibres and from 25 to 75 μm for the type 2 fibres. No other structural or histochemical abnormalities were seen.

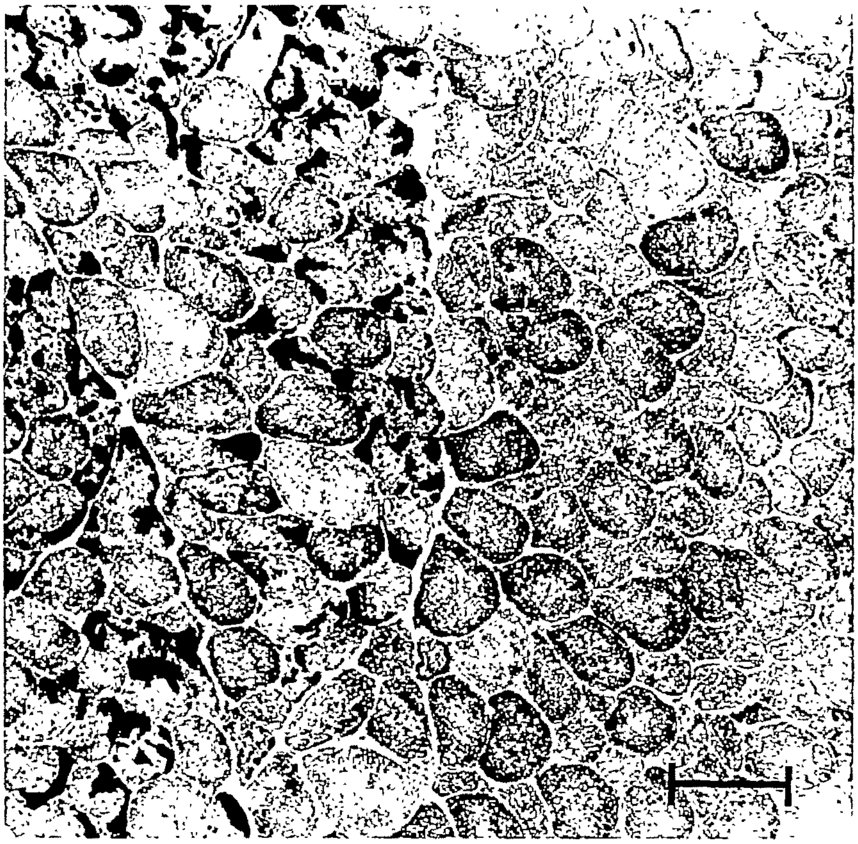

FIG. 2. Left triceps muscle to show tubular aggregates in a high proportion of the type 2 muscle fibres in some fascicles with relative sparing of others. NADH-tetrozolium reductase. Bar = 100 μm.

External intercostal muscle. The changes were similar although the tubular aggregates were smaller, more peripherally placed and were less numerous (fig. 4).

Acetylcholine esterase activity. End-plates from the patient's intercostal muscle stained with the Karnovsky-Roots method are shown in fig. 5B. There was abundant acetylcholine esterase activity and the distribution of the enzyme more closely resembled the normal configuration (fig. 5A) than that usually seen in myasthenia gravis (fig. 5C).

Electron Microscopy

Right triceps muscle. In transverse sections, numerous muscle fibres contained large aggregations of tubules. They were usually centrally located and circular in outline, but small subsarcolemmal aggregates were also present. The aggregates

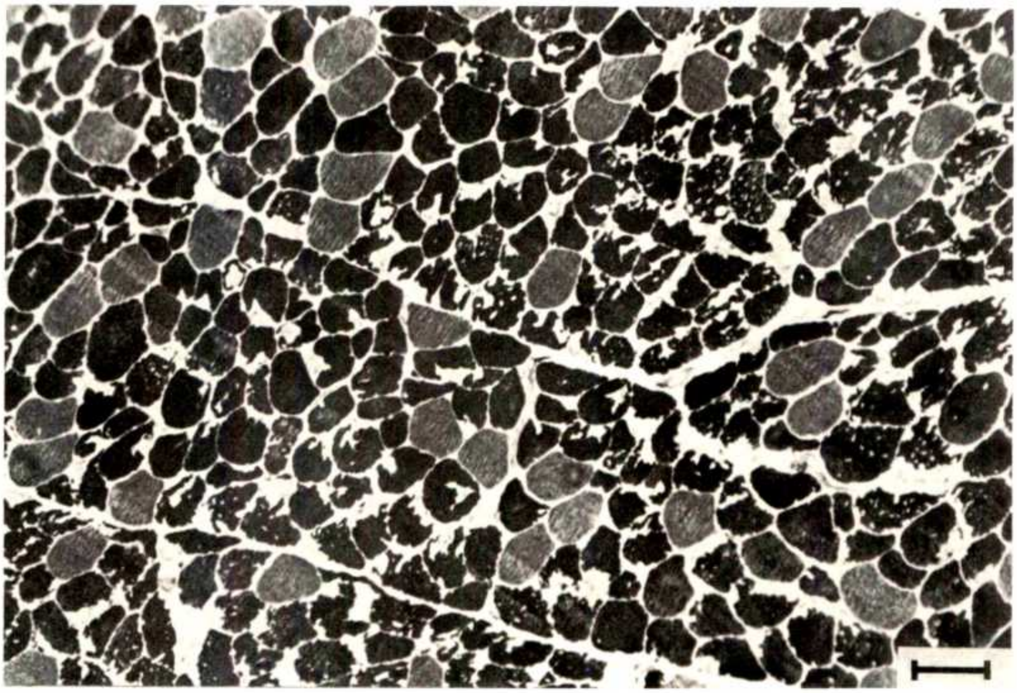

FIG. 3. Left triceps muscle to show that the tubular aggregates lacked myofibrillar material and were confined to the type 2 muscle fibres. Myofibrillar ATPase reaction pH = 9.4. Bar = 100 μm.

contained many tightly packed fascicles of tubules having a predominantly longitudinal orientation. The narrow interstices between individual fascicles were filled with glycogen granules. The tubules demonstrated the various forms which have been described previously. They consisted of the following types: (1) a simple pair of concentric tubules (fig. 6A); (2) paired tubules with a central dense core (fig. 6A); (3) an outer tubule enclosing an amorphous core of similar diameter to the standard inner tubule (fig. 6B); (4) a large outer tubule containing up to four or more standard-sized inner tubules (fig. 6C). Throughout the aggregates connections could be found between the tubules and the terminal cisterns of the sarcoplasmic reticulum. In many instances they could be seen to make triad-like junctions with elements of the transverse tubular system.

External intercostal muscle. The aggregates were less numerous but smaller and tended to be peripherally located within large subsarcolemmal accumulations of glycogen (fig. 6A). In both biopsies affected fibres contained unusually large numbers of lipid droplets, occasional masses of lipofuscin and increased amounts of intermyofibrillar glycogen.

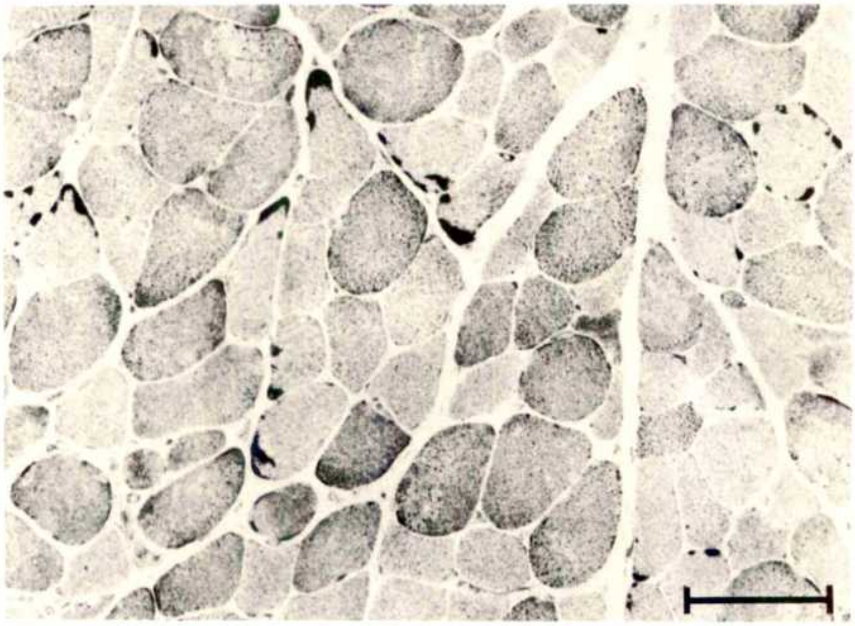

FIG. 4. Left ninth external intercostal muscle. Note the presence of small, peripherally-placed, tubular aggregates in a proportion of the type 2 fibres. NADH-tetrazolium reductase. Bar = 100 μm.

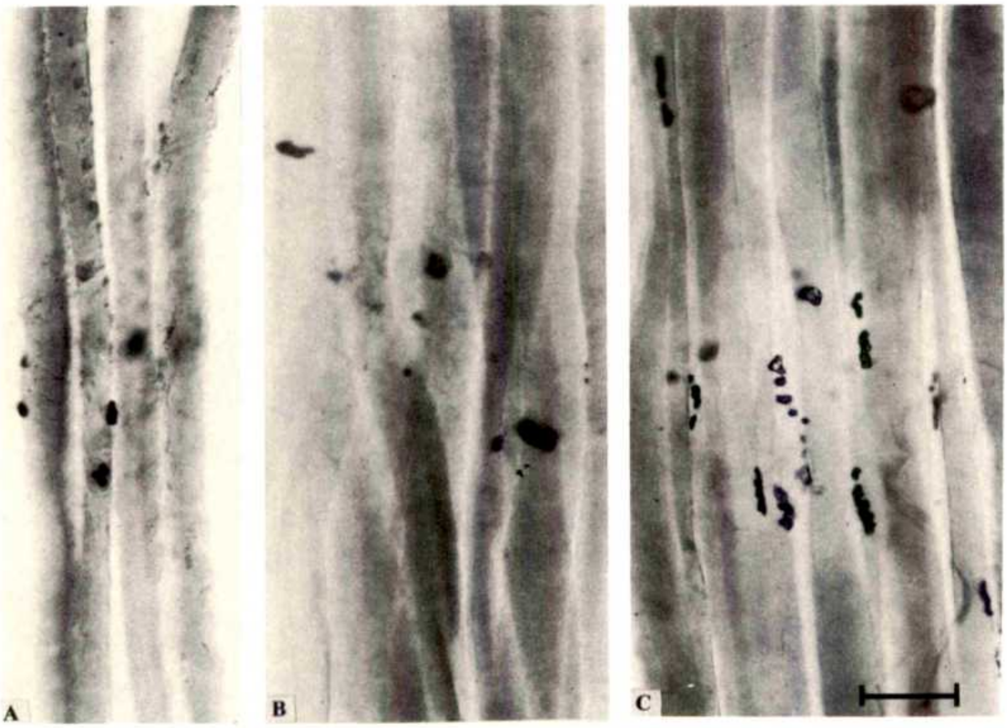

FIG. 5. End-plates stained with the Karnovsky-Roots method to show acetylcholinesterase activity. A, control muscle; B, patient A.A.; C, patient with myasthenia gravis. Bar = 100 μm.

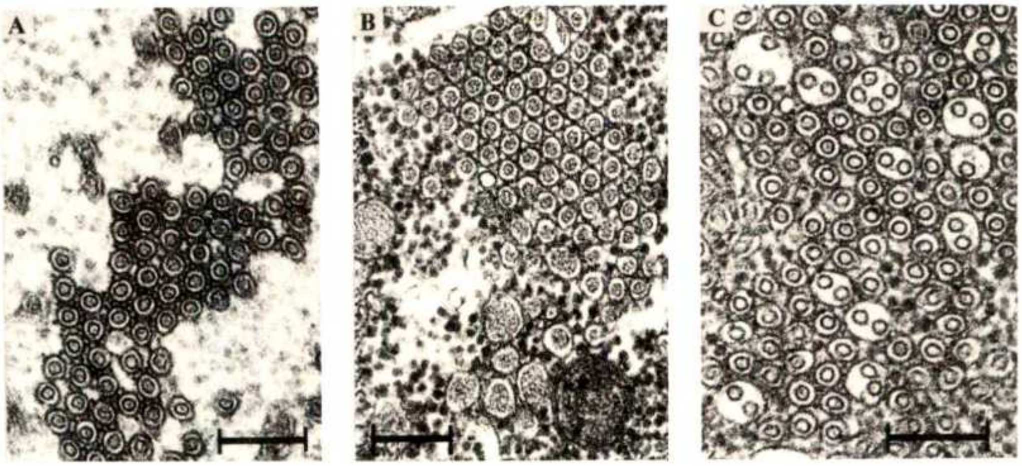

FIG. 6. Electron micrographs of tubular aggregates. A, from intercostal muscle to show pairs of closely-packed concentric tubules, some with central dense cores, embedded in glycogen granules; B, from left triceps. Note that the inner element of each pair of concentric tubules is replaced by a granular central rod of material which closely resembles the content of adjacent smooth endoplasmic reticulum; C, left triceps to show some enlarged outer tubules containing up to four inner tubules. Bar = 0.2 μm.

End-plates and nerves. A few motor end-plates of varying morphology and small intrafascicular nerve fibre bundles were found within the intercostal biopsy. The nerve terminals at some neuromuscular junctions contained distended mitochondria, phospholipid membrane-containing secondary lysosomes, and small numbers of synaptic vesicles. The post-synaptic portions of these junctions were characterized by sparse and irregular junctional folds of varying depths, both branched and unbranched, within a sole-plate devoid of mitochondria and other formed organelles except 10 nm filaments and microtubules (fig. 7). Other end-plates possessed nerve terminals well supplied with synaptic vesicles and were associated with sole-plates having a normal complement of post-synaptic folds (fig. 8). No tubular aggregates were seen in association with these endings. The intrafascicular myelinated and unmyelinated nerve fibres and their sheaths showed no obvious fine structural abnormalities.

Junctional Acetylcholine Receptors

A saturation time curve for the binding of ^{125}I-α-bgtx to the patient's AChR is shown in fig. 9, and is compared with pooled data from 4 control subjects and 3 adults with autoimmune myasthenia gravis. Results of experiments on a larger number of controls and myasthenic subjects, using a wide range of toxin concentrations and incubation times are summarized in Table 1. With 50 nmol/l ^{125}I-α-bgtx, the patient's receptors reached saturation at 9.9 attomoles per end-plate. This figure is comparable to results obtained in 16 patients with myasthenia

TABLE 1.

Summary of binding data from patient A.A., from controls and from patients with myasthenia gravis. In experiments on control and myasthenic AChR, ^{125}I-α-bgtx concentrations ranged from 50 to 200 nmol/l and those for tubocurarine ranged from 0.1 to 100 μmol/l.

	Attomoles of ^{125}I-α-bgtx bound per end-plate		*No. of toxin binding sites per end-plate* $\times 10^7$		$k_{+1} \times 10^4\ M^{-1}s^{-1}$		*I_{50} for d-tubocurarine*
	range	*mean ± SD*	*range*	*mean ± SD*	*range*	*mean ± SD*	(μ*mol/l*)
Control	13.4-31.8	22.07 ± 5.46 (n = 16)	0.8-1.91	1.32 ± 0.31	1.1-3.0	1.92 ± 0.6 (n = 11)	0.41, 0.25
Myasthenia gravis	1.7-13.1	5.64 ± 3.42 (n = 16)	0.1-0.79	0.34 ± 0.21	0.5-2.8	1.79 ± 0.68 (n = 14)	0.49, 0.40, 0.26
Patient A.A.		9.9		0.6		1.5	0.03

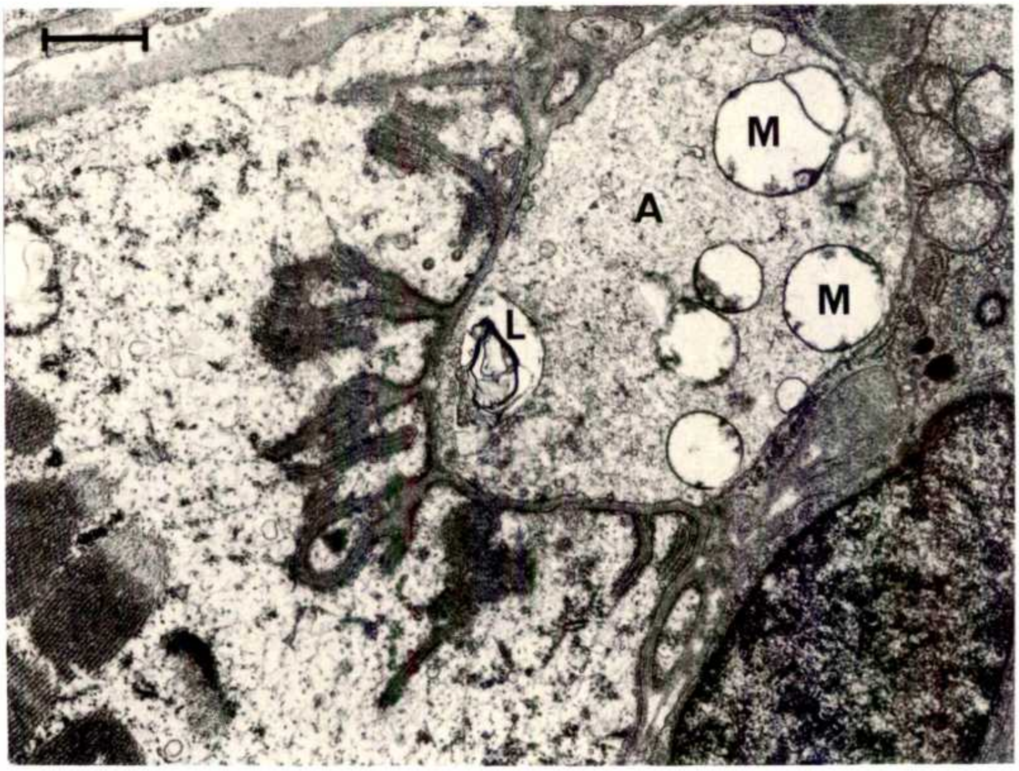

FIG. 7. Transverse section through a neuromuscular junction of an intercostal muscle fibre. The axon terminal (A) contains numerous filaments, some distended mitochondria (M) and secondary lysosomes (L) but very few synaptic vesicles. The sole-plate contains few recognizable organelles and the post-synaptic folds are relatively shallow and few in number. Bar = 1 μm.

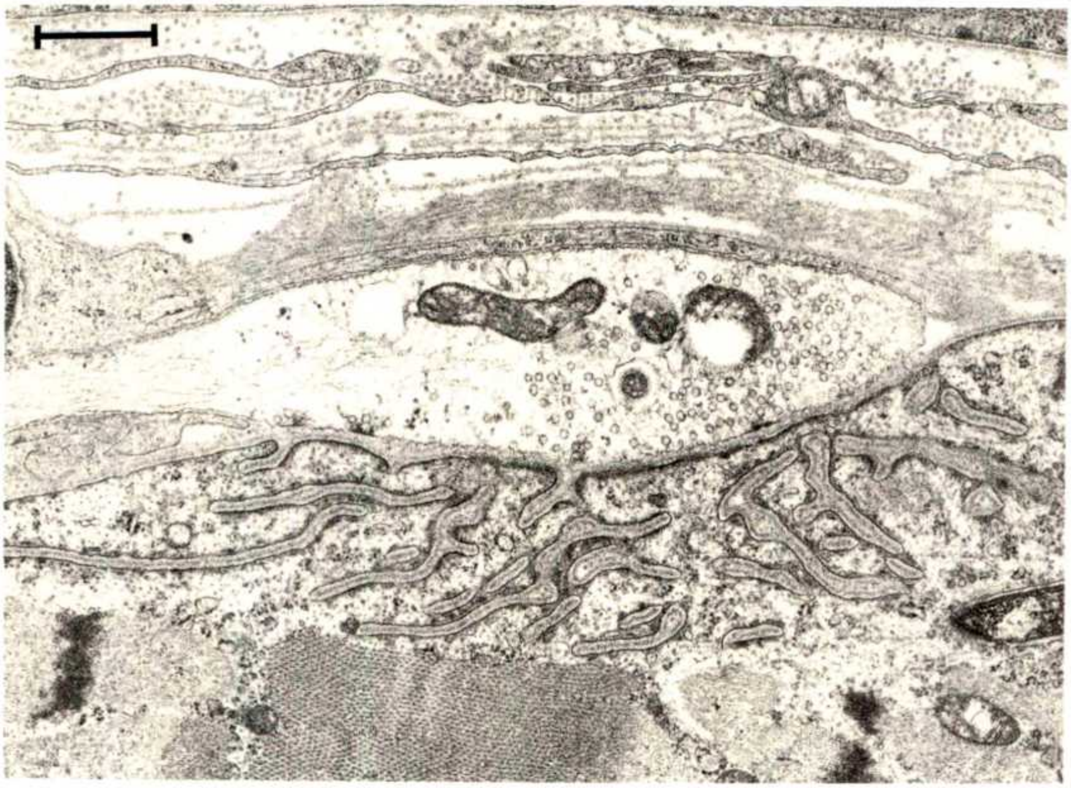

FIG. 8. An example of a more normal neuromuscular junction from the intercostal muscle of patient A.A. The axon terminal is well provided with synaptic vesicles and the post-synaptic folds are extensive and branched. Bar = 1 μm.

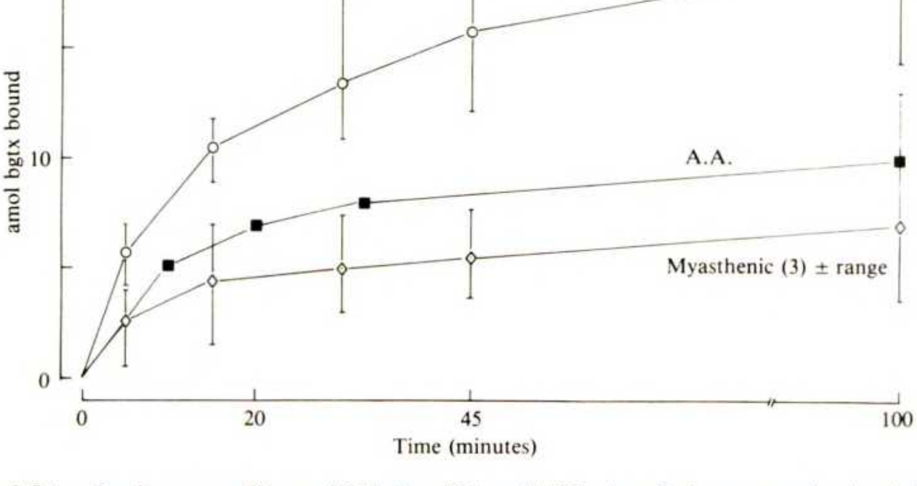

FIG. 9. Saturation time curves of the specific binding of 50 nmol/l ^{125}I-α-bgtx. Ordinate-attomoles of toxin bound per end-plate. Patient A.A. ■; mean and range in 4 controls ○; mean and range for 3 patients with myasthenia gravis ◇.

gravis where, with different toxin concentrations, saturation values ranged from 1.7 to 13.1 attomoles per end-plate (mean 5.65 SD ± 3.42). Under the same conditions of incubation saturation values for 16 controls were significantly higher and ranged from 13.4 to 31.8 attomoles per end-plate (mean 22.07 SD ± 5.46). The calculated number of toxin binding sites per end-plates was 0.6×10^7 for patient A.A., (45 per cent of mean control value) compared with a range of 0.1 to 0.79×10^7 in patients with myasthenia gravis (8 to 60 per cent of mean control value). The rate of toxin binding to the patient's AChR was similar to rates obtained both in controls and myasthenic subjects, the association rate constant (k_{+1}) being 1.5×10^4 M^{-1} s^{-1} (*see* Table 1).

On the basis of the toxin binding studies alone, the patient's receptors were indistinguishable from those occurring in myasthenia gravis. However, studies of the inhibitory effects of d-tubocurarine on the rate of toxin binding revealed significant changes in receptor affinity which were not found in control or myasthenic subjects. The results of these experiments are shown in the form of a logarithmic plot of $(r-1)/_I$ in fig. 10. The I_{50} for d-tubocurarine was similar for both control and myasthenic AChR with values of 0.40 and 0.25 μmol/l in 2 controls, and 0.49, 0.40 and 0.26 μmol/l in 3 patients with myasthenia gravis. With the patient's receptors, however, the same degree of inhibition of toxin binding occurred with

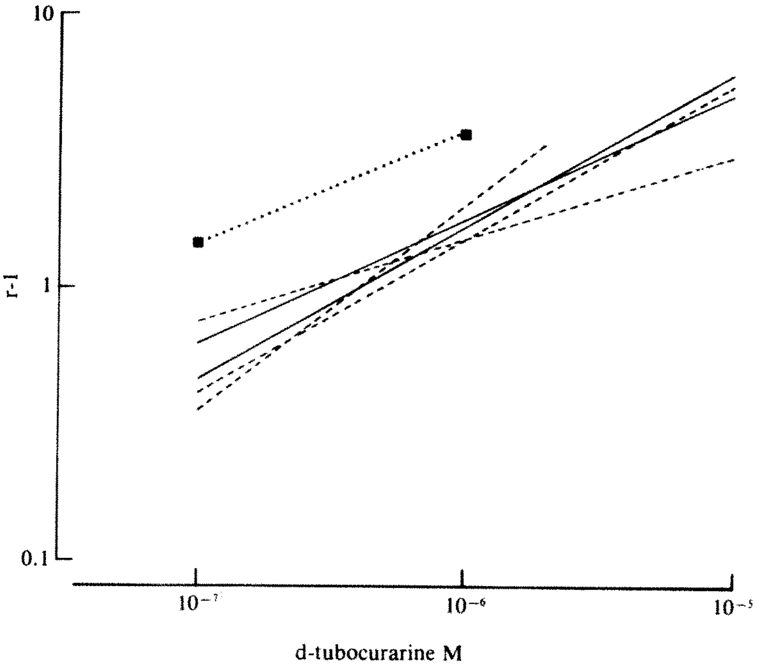

FIG. 10. Plot showing inhibition in the rate of ^{125}I-α-bgtx binding by d-tubocurarine. Patient A.A. . . .; 2 control patients ——; 3 patients with myasthenia gravis ----. Plots were drawn by linear regression. Correlation coefficients were 0.99 for normals and 0.99, 0.95, 0.80 for myasthenia gravis.

approximately ten-fold lower concentrations of tubocurarine (*see* fig. 10 and Table 1). Because of this, tubocurarine concentrations used in these experiments were in excess of the I_{50}. Extrapolation of the data plotted in fig. 10 gives an I_{50} value for the patient's receptors of 0.03 μmol/l. With 100 μmol/l tubocurarine concentration there was complete inhibition of specific toxin binding.

These results indicated that, as in myasthenia gravis, the patient's receptors were significantly reduced in number and showed a normal affinity of binding for ^{125}I-α-bgtx. In contrast to the findings in myasthenia gravis, however, the patient's receptors showed a ten-fold increase in the affinity of binding for d-tubocurarine.

DISCUSSION

Neonatal and juvenile myasthenia and myasthenia gravis of adult onset are now known to be associated with circulating antibody directed against the nicotinic junctional AChR (Almon, Andrews and Appel, 1974; Mittag, Kornfeld, Tormay and Woo, 1976; Vincent and Newsom-Davis, 1980). Anti-AChR-antibody is thought to exert its effect of reducing the number of functioning AChR by inducing complement-mediated damage at the post-synaptic membrane and by increasing the rate of AChR degradation (Drachman, Angus, Adams, Michelson and Hoffmann, 1978; Drachman, Adams, Stanley and Pestronk, 1980). Although pharmacological blocking of AChR by antibody has been demonstrated experimentally (Shibuya, Mori and Nakazawa, 1978) its role in the pathogenesis of the transmission defect in human myasthenia gravis remains uncertain.

Much less is known about the mechanisms underlying altered neuromuscular transmission in the congenital, familial infantile and limb girdle forms of myasthenia (Fenichel, 1978; Patten, 1978; Robertson, Chun and Kornguth, 1980). These conditions characteristically present in infancy or childhood, usually run a more benign non-progressive course and do not appear to be antibody-mediated (Patten, 1978; Vincent and Newsom-Davis, 1979). They commonly show some response to anticholinesterase drugs but limited data indicate that they are not helped either by thymectomy or by steroid treatment.

Studies mainly from A. G. Engel's laboratory point to the existence of several congenital myasthenic syndromes each with its own specific type of junctional defect (Engel, 1980). One patient reported by this group showed absence of end-plate acetylcholinesterase activity with reduced size of nerve terminal and minimal increase in the density of synaptic vesicles (Engel, Lambert and Gomez, 1977). In a family with four affected siblings, the defect appeared to be presynaptic and possibly involved either the uptake of choline by the nerve terminals or the synthesis or packaging of neurotransmitter (Hart, Sahashi, Lambert, Engel and Lindstrom, 1979). Another patient with a possible defect of ACh synthesis has since been described (Vincent, Cull-Candy, Newsom-Davis, Trautmann and Molenaar, 1981). Engel and his group have also postulated a third type of transmission defect involving the ACh-induced ion channel in three adult males with a familial myasthenic syndrome (Engel *et al.*, 1979). As in the patient with AChE deficiency, electromyographic studies showed a decremental response at 3 Hz and repetitive firing of the muscle in response to a single nerve stimulus. Microelectrode studies revealed markedly prolonged epp's and mepp's, normal quantum content of the epp and a low normal or reduced mepp amplitude. Nerve terminals were reduced in size and were associated with degeneration of junctional folds and loss of AChR. Muscle biopsy showed tubular aggregates, type I muscle fibre predominance and group atrophy. Tubular aggregates have also been described in two other families with a myasthenic syndrome restricted to the limb girdle musculature (Johns *et al.*, 1973; Dobkin and Verity, 1978), but in these cases the nature of the transmission defect was not determined.

The combination of parental consanguinity, tubular aggregates on muscle biopsy and the death of two siblings in early infancy provides strong indirect evidence that the transmission defect in the present case was genetically determined. The mild non-progressive nature of the disease, the suggestion of exercise intolerance in childhood and the absence of anti-AChR-antibody are also in keeping with a familial type of myasthenic disease. However, the pattern of inheritance, clinical features, the lack of repeat firing of the muscle in response to a single nerve stimulus and the muscle biopsy appearances distinguished this patient from the cases described by Engel *et al.* (1979).

End-plate studies showed an abundance of normally distributed AChE but variable junctional morphology under the electron microscope. Some neuromuscular junctions possessed relatively normal-looking nerve terminals, well supplied with synaptic vesicles and sole-plates exhibiting a full complement of post-synaptic folds. In others, however, the nerve terminals were abnormal with reduced numbers of synaptic vesicles and the sole-plates were devoid of mitochondria and contained sparse, shortened and irregular junctional folds. Although tubular aggregations were plentiful in the non-end-plate regions of the intercostal muscle fibres they were never seen in the vicinity of the post-junctional folds.

Radiochemical studies using di-iodinated ^{125}I-α-bgtx revealed that the number of junctional AChR was reduced to within the range obtained in myasthenia gravis (Lecky and Morgan-Hughes, 1981). Unlike the findings in myasthenia gravis, however, this patient's receptors exhibited a ten-fold increase in their affinity for d-tubocurarine. Although our studies have shown decreased agonist binding to a proportion of ^{125}I-α-bgtx binding sites in some patients with myasthenia gravis, receptor affinity for both agonists and antagonists as given by the I_{50} values (which are independent of the number of AChR) did not differ from that found in control muscle (Lecky and Morgan-Hughes, 1981). The markedly increased affinity of this patient's AChR for d-tubocurarine was not seen either in controls or in patients with myasthenia gravis and provides strong evidence for an abnormality of the AChR macromolecule. Such an abnormality could be due to a genetic defect of AChR biosynthesis, a change in the configuration of the receptor molecule or an altered membrane environment. It is perhaps relevant that the responses of AChR to individual cholinergic ligands may be increased or decreased by a reduction of receptor protein brought about by dithiothereitol (Karlin, Cowburn and Reiter, 1973). An increased affinity of AChR for ^{3}H-ACh, without a change in the number of binding sites, has also been demonstrated by treatment of AChR-rich torpedo membrane fragments with detergent (Brisson, Devaux and Changeux, 1975). These changes in receptor affinity were attributed to alterations in their lipid membrane environment. It is possible that some intracellular biochemical defect operating in this patient could similarly alter the properties of the AChR and also lead to a reduction in their number. Such a defect might also involve other membrane components of the muscle cell thereby leading to the formation of tubular aggregations.

SUMMARY

This paper reports the findings in a 32-year-old man who presented in adult life with a myasthenic syndrome characterized by dysphagia, dysphonia, fluctuating ptosis, episodic diplopia and a variable weakness of the limbs and trunk. Electromyography showed a small decremental response, increased neuromuscular jitter and blocking of some components. Histochemical and electron microscopic studies revealed changes in end-plate morphology and prominent tubular aggregations within the muscle fibres. Radiochemical investigations using di-iodinated ^{125}I-α-bungarotoxin demonstrated a reduction in the number of AChR and alterations in receptor affinity which suggested an abnormality of the AChR macromolecule.

ACKNOWLEDGEMENTS

We are indebted to the Muscular Dystrophy Group of Great Britain for generously supporting this work and to Mr Richard Hayward and Mr Marvin Sturridge for kindly performing the muscle biopsies. Miss Marjorie Ellison and Mr Brian Young provided technical assistance.

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ON THE PATTERN OF CHANGES IN THE RAT NERVOUS SYSTEM PRODUCED BY 2,5 HEXANEDIOL

A TOPOGRAPHICAL STUDY BY LIGHT MICROSCOPY

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INTRODUCTION

THE neurological disturbances caused by certain hexacarbon compounds in man (Astbury, Nielsen and Telfer, 1974; Herskowitz, Ishii and Schaumburg, 1971; Mendell, Saida, Ganansia, Jackson, Weiss, Gardier, Christman, Allen, Couri, O'Neil, Marks and Hetland, 1974) and in animals (Spencer and Schaumburg, 1975, 1976, 1977) are related to the accumulation of 10 nm neurofilaments within axons, a process very similar to the effects of chronic carbon disulphide intoxication (Szendzikowski, Stetkiewicz, Wrońska-Nofer and Zdrajkowska, 1973; Cavanagh, Szendzikowski and Wrońska-Nofer, 1978). This might be thought to be of purely academic interest if it were not for the recent description of cases of giant axonal neuropathy in man (Astbury, Gale, Cox, Baringer and Berg, 1972; Carpenter, Karpati, Andermann and Gold, 1974; Igisu, Ohta, Tabira, Hosokawa, Goto and Kuroiwa, 1975) and in dogs (Duncan and Griffiths, 1977, 1979) a condition which also has as its basic pathological feature similar accumulations of 10 nm neurofilaments within axons of the peripheral and central nervous systems. Unfortunately because there has not yet been published a systematic survey of the pathological changes produced by hexacarbon compounds in the nervous and other tissues of experimental animals, there is some uncertainty as to the nosological position of this intoxication, particularly with regard to certain other now fairly well-defined neurointoxications. In view of the practical importance of this experimental system for the further study of neurofilamentous diseases, it was thought timely to follow the evolution of the pathological changes in the rat using conventional neuropathological techniques for light microscopy, for these time-honoured techniques not only allow for topographical surveys to be easily made, but because of the affinity of neurofilaments for silver stains the specific feature of this particular intoxication can be readily appreciated.

MATERIALS AND METHODS

Twenty-two male and female rats weighing from 175 to 250 g were caged in pairs and fed diet 41B (Chardex) and allowed free access to water in which 2,5 hexanediol (2,5 HDol; Aldrich Chemical Co. Ltd.) was dissolved in 2 or 1 per cent concentration. Two male rats were put into metabolism cages and their food and water intake and their excretions measured daily. The rest were housed in plastic boxes. All animals were weighed and the water levels in the bottles recorded daily, from which the average dose per animal per day could be calculated (Table 1), and all were daily examined for general functional changes and put through simple tests of neurological function.

The animals were killed by perfusion of fixative into the ascending aorta at a pressure of 180 mmHg while under deep ether anæsthesia. The fixatives used were glutaraldehyde 4 per cent in 0.1 M cacodylate buffer for the preparation of teased peripheral nerve fibres and for electron microscopy (not reported here) or 10 per cent formaldehyde with 2 per cent acetic acid for embedding in paraffin wax. The CNS tissues fixed in glutaraldehyde were rapidly transferred to 10 per cent formalin if they, too, were to be paraffin-embedded. Exposure to glutaraldehyde for more than an hour or two leads to considerable hardening of the tissues, making sectioning in paraffin difficult. Paraffin sections were stained with hæmatoxylin and eosin, gallocyanin chrome-alum, or by Glees and Marsland's silver stain for axons. This last, if properly done, and when fixation is good, impregnates most axons, and many preterminal fibres as well as boutons terminaux. Filamentous accumulations are particularly well stained. Indeed, the images obtained are remarkably similar to immune fluorescent stains using antibodies to neurofibrillary antigens (B. H. Anderton, personal communication).

Blocks for light microscopy were taken thus: cerebrum (coronal) ×3, cerebellum (sagittal and parasagittal) ×4, brain-stem (TS) ×5, cervical cord (TS) ×4, thoracic cord (TS) ×3, lumbosacral cord (TS) ×4, cervical spinal ganglia (LS) ×3, lumbar spinal ganglia (LS) ×3, sciatic nerve (LS), posterior tibial nerve (LS), anterior tibial muscles (TS), gastrocnemius and suralis muscles (TS), foot muscles (LS), the eye, including oculomotor muscles, diaphragm, tongue (TS) ×3 including hypoglossal nerve, masseter (TS) including facial nerve, and general body organs including testis.

Peripheral nerves were teased in cedar wood oil after overnight staining in osmium tetroxide. For electron microscopy tissues were dehydrated in alcohols and passed through propylene oxide to Epon.

RESULTS

Functionally, there was steady weight loss while the animals were on 2 per cent 2,5 HDol and an occasional animal died if this was continued long beyond two weeks. After fourteen days, therefore, the concentration was reduced to 1 per cent. The two animals in the metabolism cages showed a drop in both water and food intake to about half normal levels, so that it might be assumed that the same was taking place in those not so carefully monitored. Some of the weight loss may be ascribed to this cause therefore. On the higher dose the animals became subdued but were easily handled, and became lively if stimulated. They walked well on a narrow rod and showed no neurological defect until about the eighteenth day when they began to show wasting of the loins and a flat-footed, waddling, clumsy gait, with some reduction of the splay reflex. They were apathetic from this time on. When put on to 1 per cent their weight remained steady and perhaps showed a slight gain.

TABLE 1. THE EVOLUTION OF FUNCTIONAL AND STRUCTURAL CHANGES ON CHRONIC DOSING WITH 2,5 HEXANEDIOL

Day of killing	*No. of animals and sex*	*Functional changes observed*	*Structural changes in*		
			PNS	*CNS*	*Testis*
14	1 F	Subdued	Nil	Nil	
18 19 21	2 M 1 F 1 F	'Paddling' action of hind-limbs Weakness of hind limbs Reduction of splay reflex	Nil	Early changes in brachia of SCQ and spino-cerebellar fibres only	Normal
25	2 M	Weakness and hypotonia as above. Loss of splay reflex	Nil	Spinocerebellar fibres	Normal
32 33	2 F 2 M	Paresis of hind limbs. Incontinence. Hypotonia. Loss of splay reflex	Numerous nodal and internodal axonal swellings in leg nerves	Many CNS tracts and nuclei affected. *See* Table 2	Testicular atrophy
38	2 M	Ditto	Ditto with scattered degenerating fibres	As in Table 2	Testicular atrophy
53	2 M	Ditto	Ditto with scattered degenerating fibres	As in Table 2	Testicular atrophy

Daily intake of water was about 10 to 15 ml/day/rat. The daily dose of 2,5 HDol on 2 per cent was thus about 200 to 300 mg/rat giving a range of 1.2 to 1.8 g/kg/day on average. It fell to about half this when on 1 per cent, although the water intake rose somewhat on this lower dose.

After thirty days, they became very poor in condition, hypotonic, walking with a paddle-like gait and showing a variable amount of weakness in the hind-limbs. Incontinence became noticeable after about five weeks, and the hind-limbs dragged or moved only feebly. The forelimbs still seemed moderately strong, and the animals became quite lively if handled and gently stimulated. Otherwise they were apathetic. Wasting of muscles was difficult to assess due to general loss of body weight.

Structural Changes

Changes in CNS axons began to be visible in Glees and Marsland preparations in animals killed at eighteen days. There was swelling of occasional axons in the cerebellar vermis, particularly fibres running through the granular layer of the nodulus and of the lobulus centralis and the lingula. These are regions where the spinocerebellar fibres end within the granular layer. Swelling of some axons in the spinocerebellar tracts in cervical cord and as these pass from medulla to the cerebellar white matter were also present at this time. No changes were unequivocally visible by light microscopy in dorsal columns or pyramids at this time, nor in any other region of the brain-stem, forebrain or spinal cord except the brachia of the superior colliculi. No changes, furthermore, could be found in many samples of teased nerves at this time.

By twenty-five days definitely swollen axons were seen in the cerebellar cortex and white matter in the same regions as before, but now definitely swollen axons were visible in the spinocerebellar tracts in the medulla and in the upper spinal cord. Again, no unequivocally swollen fibres were evident in any other region of the CNS, nor in any of a large number of peripheral nerves sampled.

At thirty-two and thirty-three days large numbers of swollen fibres which stained heavily with silver were seen in many regions of the CNS. These are listed in Table 2 and they all seemed to develop more or less equally during the eight-day interval from the previous time of twenty-five days. Animals examined at thirty-eight and fifty-three days showed a virtually identical distribution of swollen fibres, the only significant difference being in the degree of swelling of axons and terminals in each region examined.

Regional Features (fig. 1)

In the cerebral cortex spindle-shaped swellings occurred on radially orientated fibres in various regions of the cortex, particularly in the parietal cortex (fig. 2) and in the parasagittal cortex (fig. 3). These spindle formations did not show any particular connection to other structures and were not confined to any one layer. Occasionally considerably thickened fibres were also found without any particular orientation and these were present in the deeper layers as well as sometimes more superficially. Neurons and glia in the cortex seemed in every way unchanged up to fifty-three days. The hippocampus rarely showed more than the occasional thickened fibre. In the corpus callosum numerous swollen fibres were visible from thirty-two days onwards. Swollen fibres were seen scattered in the fornix close to the mammillary bodies, but rarely near the hippocampus. Swollen preterminals in the mammillary bodies were frequent after thirty-three days.

Particularly striking from thirty-two days onwards was the considerable and general enlargement of axons in the fibres of the brachia of the superior colliculi (fig. 4). These fibres pass from the optic chiasm round the brain-stem to terminate in the superior colliculus and this seems to be an important pathway in the rat. Large numbers of hugely swollen fibres were a striking feature from thirty-two days onwards in this region and with time this extended in a retrograde manner towards

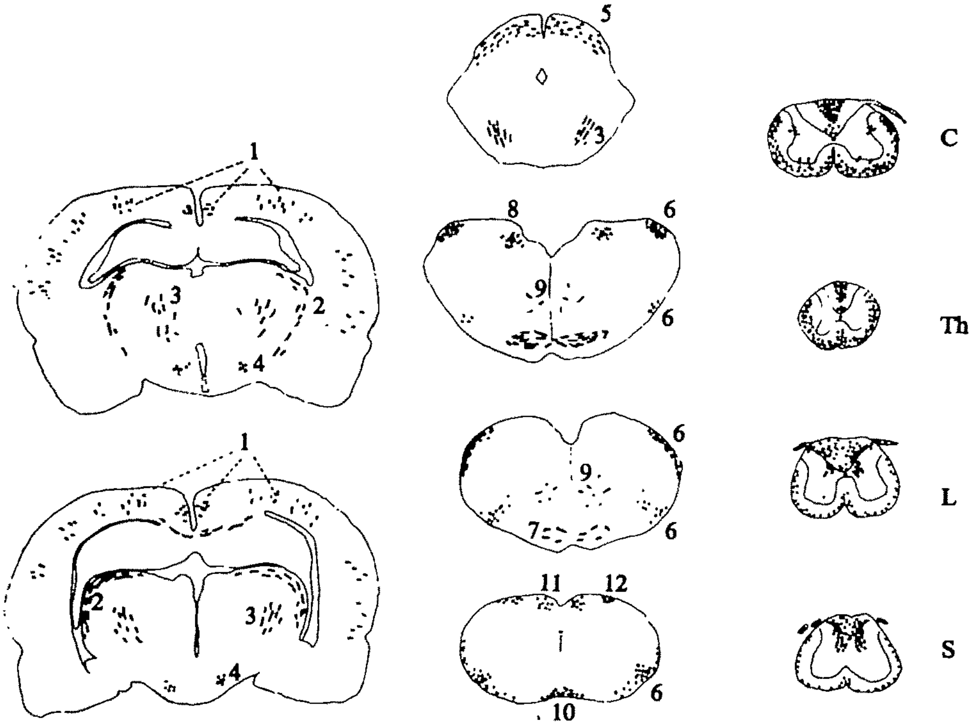

FIG. 1. Diagram of the distribution of the principal affected fibres from one month onwards. 1. Radial and other cortical fibres with corpus callosum. 2. Brachium of the superior colliculus (optic tracts). 3. Lateral lemniscus and terminals in ventral thalamus. 4. Fornix of hippocampus. 5. Terminals in colliculi. 6. Spinocerebellar tracts. 7. Decussation of trapezoid body and superior olives. 8. Terminals in vestibular nuclei. 9. Fibres in the reticular formation. 10. Pyramidal tracts. 11. Gracile nuclei. 12. Cuneate nuclei. In spinal cord, dorsal columns severely affected in gracile tracts, less in cuneate. In lumbosacral regions (L and S) swollen fibres in dorsal roots, in middle root entry zones, and in dorsomedial nuclei. In cervical (C) region fibres entering grey matter affected. Th = thoracic. Pyramidal tracts in base of dorsal columns affected throughout. Ascending and descending fibres affected in lateral and ventral tracts throughout.

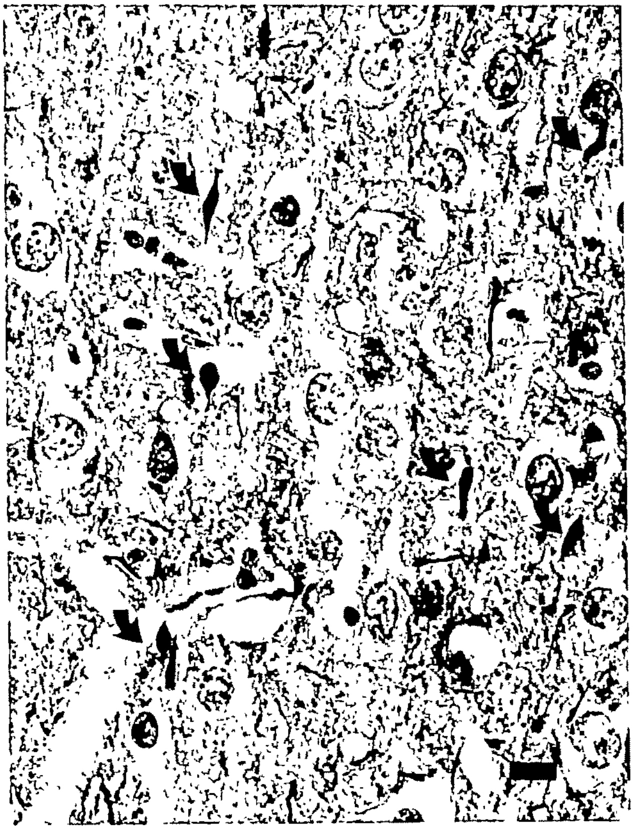

FIG. 2. Spindle-shaped swellings (arrows) in radial fibres running through the cerebral cortex. They were not associated with any particular structure, and nerve cells showed no changes. Glees and Marsland. Bar = 10 μm.

the optic chiasm, but even at fifty-three days few actual chiasmatic fibres were swollen. No optic nerve fibres were ever found to be affected in this way and the retina and its ganglion cells always appeared normal.

In the upper brain-stem the lateral lemniscus was constantly affected from thirty-two days, but not to the same degree as in the optic pathways. The ventral nuclei of the thalamus showed swollen preterminals and boutons terminaux, just as did the lateral geniculate bodies.

Further caudally, the pons and medulla came to develop striking changes in many systems. Apart from the spinocerebellar tracts (fig. 5) which began to be affected at the eighteenth day, the tectospinal tracts showed many swollen fibres as did the corticospinal tracts, the latter particularly evident at their decussation in the lower medulla (figs. 7 and 8). In vestibular nuclei there were many swollen preterminals and boutons from thirty-two days onwards and in the ventral cochlear pathways through the trapezoid decussation and into the superior olives, there were also

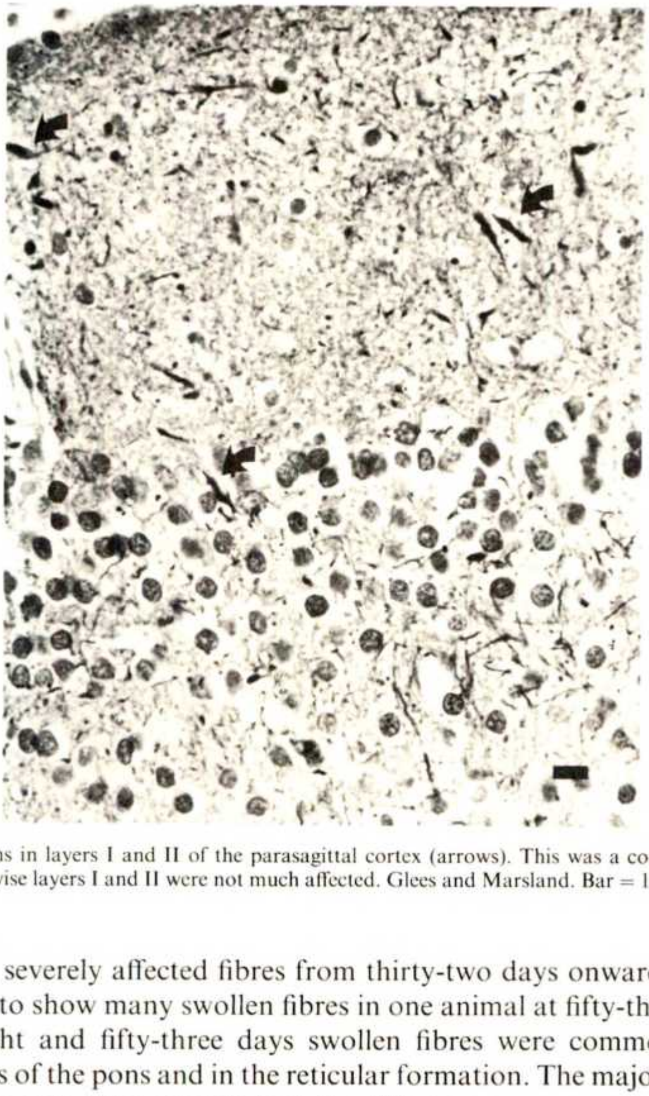

FIG. 3. Swollen axons in layers I and II of the parasagittal cortex (arrows). This was a consistent finding, but otherwise layers I and II were not much affected. Glees and Marsland. Bar = 10 μm.

constantly and severely affected fibres from thirty-two days onwards. The VIIIth nerve was seen to show many swollen fibres in one animal at fifty-three days.

At thirty-eight and fifty-three days swollen fibres were common among the transverse fibres of the pons and in the reticular formation. The major cranial nerve nuclei were not especially altered, but the Vth nerve sensory nuclei had many swollen preterminals and boutons in the thirty-eight and fifty-three day animals.

The cerebellum had evidence of involvement of efferent as well as afferent fibres. The spinocerebellar pathways were spectacularly swollen in the later stages and even degenerating fibres were occasionally seen, but these were very few. From thirty-two to fifty-three days, swollen, densely-staining fibres were seen in the white matter of the folia in moderate numbers, in the granular layer not infrequently, and the climbing fibres running upon the virtually unstained dendrites of the Purkinje cells were often more intensely stained and thicker than in normal animals. Basket cell fibres were also frequently more intensely stained than normally.

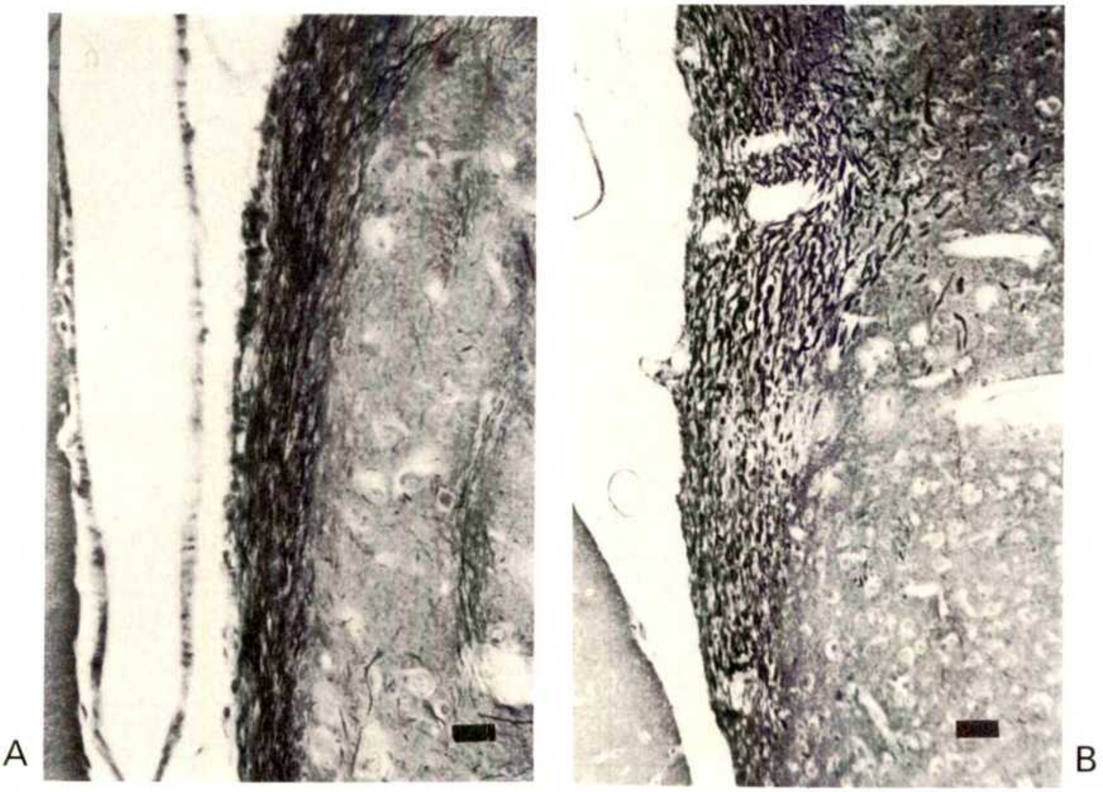

FIG. 4A, normal brachium of the superior colliculus made up of moderate thin axons. Glees and Marsland. Bar = 20 μm. B, abundant swollen fibres in the brachium of the superior colliculus. Glees and Marsland. Bar = 40 μm.

Of particular interest to students of human neuropathology was the frequent occurrence of 'torpedoes' upon the axons of Purkinje cells (fig. 6). These deeply-staining, oval swellings were found haphazardly through the cortex lying beneath the Purkinje cell layer: they were once found on day eighteen, and on a few occasions at the twenty-fifth day, but were numerous thereafter. As further evidence of involvement of Purkinje cell axons, the preterminal fibres and the boutons within the dentate and other roof nuclei of the cerebellum were swollen, often substantially, from thirty-two days onwards.

In the spinal cord, the earliest finding of swollen fibres was in the cervical spino-cerebellar tracts on the eighteenth and nineteenth days, but from thirty-two days onwards more spectacular changes were evident, affecting many fibre pathways over the greater part of the cord.

Dorsal columns showed changes at all levels, most pronounced in the gracile tracts; occasionally swollen fibres were evident also in the cuneate tracts. In the cervical region the gracile tracts were principally affected but in the lumbar region

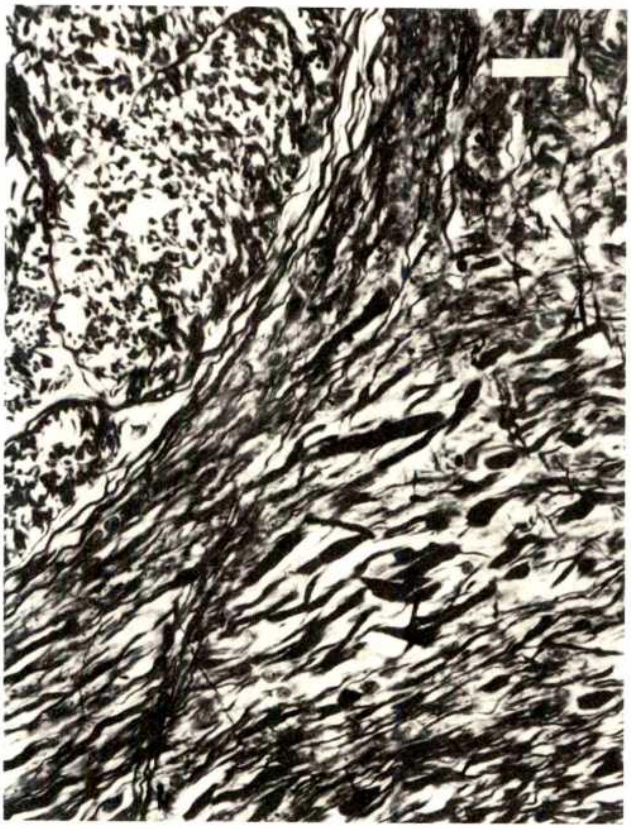

FIG. 5. Swollen fibres in the spinocerebellar tract entering white matter of the cerebellum. Glees and Marsland. Bar = 50 μm.

the fibres in the middle root zone as they entered from the dorsal roots were also noticeably swollen. Indeed the local branches of these entering fibres were strikingly swollen and deeply staining as they ran to terminate in the dorsomedial nuclei, intermediate zones, and in the anterior horns of grey matter (fig. 9). Swollen axons were commonplace from thirty-two days onwards in the dorsal roots, but these were never seen in the ventral roots.

In the lateral columns of the spinal cord swollen axons were particularly visible in the dorsolateral parts at twenty-five and thirty-two days, but after this they were visible all around the lateral tracts, and in view of the poor anatomical identification of these pathways it is difficult to know their real nature and origins. Swollen fibres were also conspicuous in the ventral tracts which are probably descending tecto-, reticulo- and vestibulo-spinal pathways, and ascending fibres to the brain-stem were also probably affected. Of particular interest was the constant involvement of the pyramidal (corticospinal) tracts lying in the base of the dorsal columns (fig. 10). This pathway showed changes all along its length from its decussation in the medulla downwards, but was probably more markedly affected in the lumbar levels than elsewhere.

Peripheral Nerves

Teased preparations were singularly unsuccessful in demonstrating any swollen paranodes or internodes in animals killed before the thirty-third day despite search in many regions. From the thirty-third day onwards, however, increasing numbers of nerve fibres with axonal swellings were evident wherever the sample was made. Since the swellings were more marked in larger fibres, nerves with a higher proportion of large fibres were more conspicuously affected (fig. 11). Of particular interest was the finding that swollen axons were apparent wherever they were sought. These were best looked for in Glees and Marsland stained paraffin sections of muscles, where mixed intramuscular nerve bundles as well as preterminal fibres

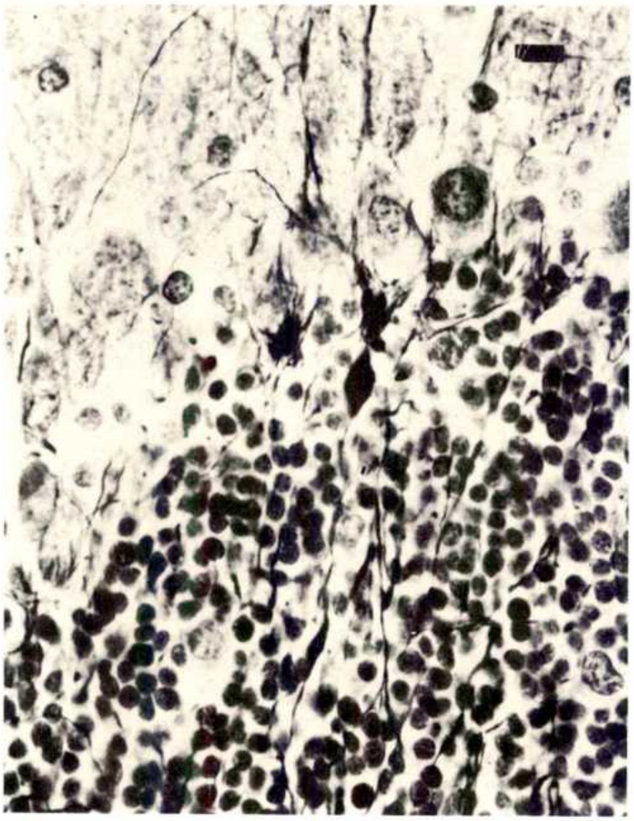

FIG. 6. Cerebellum showing typical 'torpedo' on axon of a Purkinje cell, the cell body of which is unstained by this method. Such 'torpedoes' are usually recognized as being swelling of this axon above its first myelin segment. Glees and Marsland. Bar = 10 μm.

were readily visible. Swollen axons were apparent in the tibialis anticus as well as the gastrocnemius and soleus muscles. They were also seen in the tongue, in the external ocular muscles, and in the diaphragm, as well as in the masseter muscles. The general emphasis of the swellings in larger diameter fibres was confirmed by teased preparations and the bundle to gastrocnemius and soleus muscles was particularly affected. Degenerating fibres were, however, very scanty if present at all before thirty-eight days when the nerves to gastrocnemius and sural muscles began to show many fibres breaking down. Peripheral nerves were, in general, however, rather less markedly affected then CNS tracts so far as axonal swelling is concerned, but later more degenerative changes were found in PNS fibres than in CNS.

Other Organs

Liver, kidneys, lung and spleen showed no specific features. However, in the testis there were marked and progressive atrophic changes from the thirty-third day onwards (fig. 12). There was cessation of spermatogenesis with, firstly, the

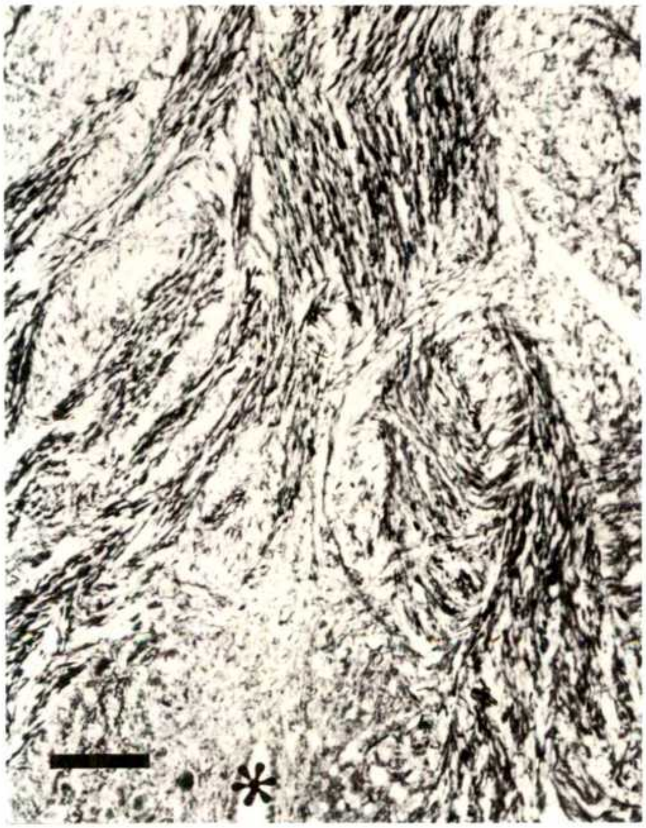

FIG. 7. Decussation of pyramids in medulla. Swollen and heavily staining fibres visible. Asterisk in central canal. Glees and Marsland. Bar = 100 μm.

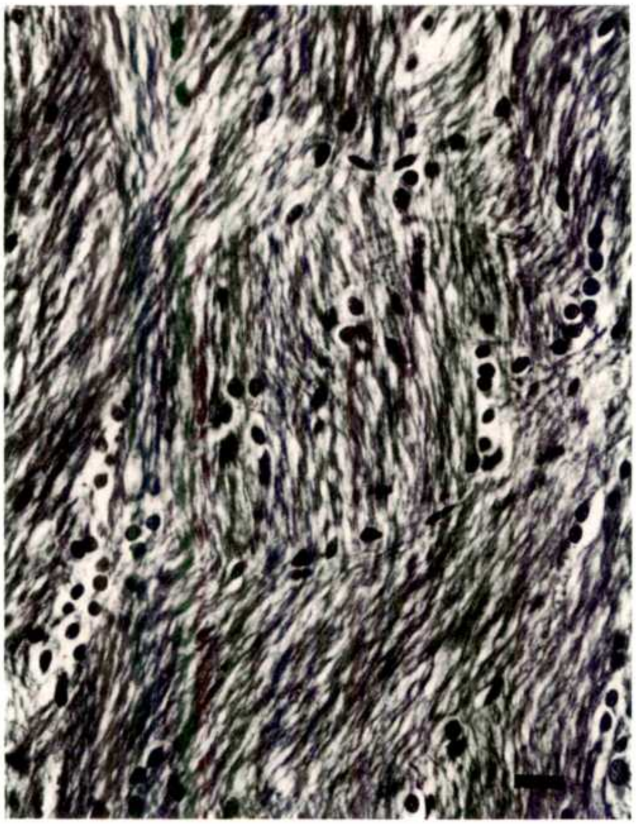

FIG. 8. Decussation of pyramids. Section adjacent to fig. 7. No evident axonal changes or change in glial nuclei. Hæmatoxylin and eosin. Bar = 20 μm.

formation of multinucleated cells due to failure of separation of the spermatids, and ultimately almost total atrophy of the cell constituents of the seminiferous tubules occurred, such that only spermatogonia and Sertoli cells remained. These changes are probably of nonspecific nature and have been observed in several other toxic and experimental circumstances, for example, after portocaval anastomosis (Kyu and Cavanagh, 1970), in p-bromophenylacetylurea intoxication (Chen and Cavanagh, 1971; unpublished data; Chen, 1973), and in dithiocarbamate intoxication (Rasul and Howell, 1974), and may have a hormonal basis.

DISCUSSION

The changes found are remarkable in not only seeming to appear more or less simultaneously in CNS and PNS after this dosing regimen during the fourth and fifth week of intoxication, but also in affecting a very wide variety of cell types with

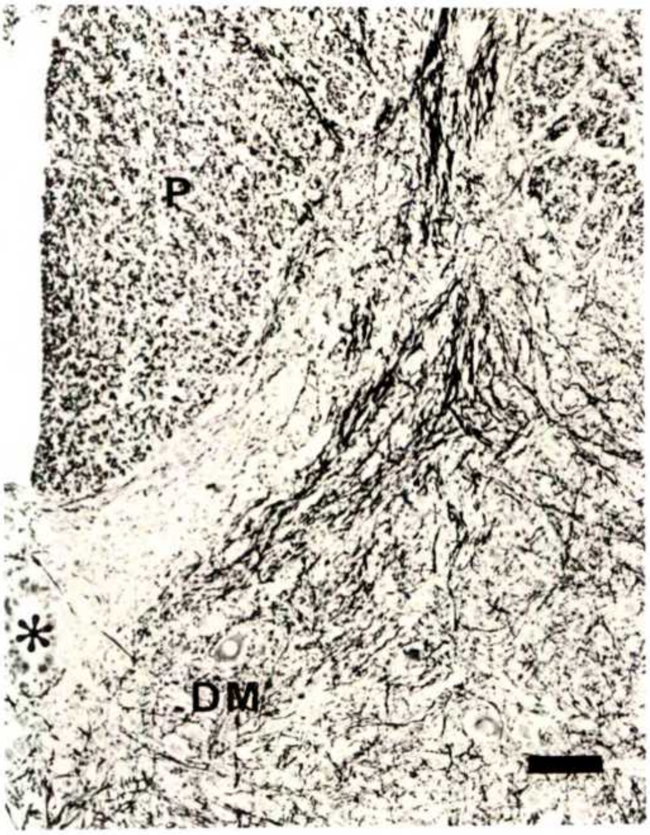

FIG. 9. Lumbar cord (transverse section). Note heavily stained fibres streaming down through the dorsal horn into the dorsomedial nucleus. The cell bodies of such fibres are in the appropriate spinal ganglion. P = posterior column. DM = dorsomedial nucleus. Asterisk in central canal. Glees and Marsland. Bar = 100 μm.

greatly differing functions and structural attributes. To some extent both fibre length and fibre size are likely to have played some role in bringing the change about. Among the first affected fibres were almost certainly the spinocerebellar which are not only among the longest in the CNS but also contain a small population of relatively large diameter (over 5 μm external diameter) fibres; the distal regions of the considerably shorter fibres of the optic pathways were also, however, affected contemporaneously. Having said that it is hard to see what these fibres have in common with, say, Purkinje cell axons which are short and relatively thin, and the fibres of the trapezoid body which is part of the cochlear-vestibular system. Moreover, in many systems the distal regions of the axons were noticeably more swollen than the proximal. This was strikingly true of the optic fibres in which the optic nerves and chiasm were virtually normal, while the more distal parts within these tracts which run around the brain-stem to the superior colliculi became hugely swollen. The same was true, to a less marked degree, of the fornix fibres. However, even this was not a general phenomenon, for pyramidal tract fibres seemed almost as much affected in the early stages at their decussation in the medulla as they were along the length of the spinal cord. Furthermore, the spinal sensory root fibres were again almost as much affected in the lumbar dorsal roots, the middle root zones and the endings within the lumbar cord as they were along the length of the gracile tracts. Swollen axons were present even within the ganglia itself at the thirty-eighth and fifty-third days. It could, therefore, not be concluded that this was passive accumulation of axoplasmic material merely at the distal ends of long fibres. The problem of swollen fibres seems not to be explicable in such simple mechanistic terms, although the degeneration that supervenes in peripheral nerves might be.

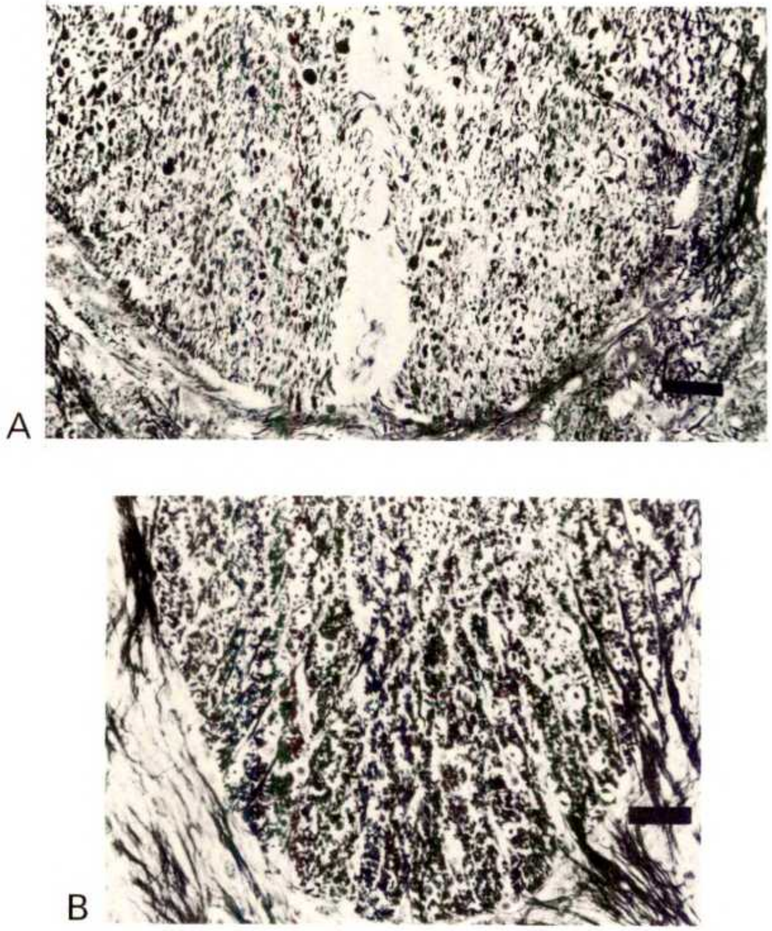

FIG. 10A, cervical cord (transverse section). Numerous swollen axons seen within pyramidal tracts. These were present at all levels studied from thirty-two days onwards. Expansion of the tract and the splitting in the midline are artefacts. Glees and Marsland. Bar = 50 μm. B, normal cervical pyramidal tract to show very regular-sized, often closely bunched, fibres. Glees and Marsland. Bar = 50 μm.

A further, very striking difference from any other previously reported intoxication, other than CS_2, is that the axonal swellings were not primarily associated with nerve fibre degeneration. In the CNS regions described above (Table 2) nerve fibre degeneration was not a significant feature in any of the affected tracts other than the gracile. There were, moreover, none of the changes associated with axonal degeneration, such as hypertrophy or hyperplasia of the astroglia or incursions of microglia, and no chromatolytic changes in the relevant nerve cell bodies, except once at a late stage in a lumbar spinal root ganglion. Nerve fibre degeneration was found, however, in peripheral nerves, particularly in certain nerves previously described by Spencer and Schaumburg (1975, 1976, 1977) in a number of reports, but the majority of axons with swellings in them were not undergoing degeneration. Except for CS_2 intoxication, this is quite unlike any previously described neurotoxic condition. Furthermore, the animals showed no specific functional disturbances relevant to the gross and widespread axonal swellings, until after the thirty-third day, when peripheral nerve fibre degeneration and degenerative changes in the gracile tracts begin to be evident. How much of the functional disturbances are relevant to actual axonal degeneration, and how much follows slowing of conduction due to myelin thinning over the swellings, and to nodal changes related to the paranodal swellings in both PNS and CNS, as well as to disturbances to synaptic transmission at all relevant points, cannot yet be stated. In view of the

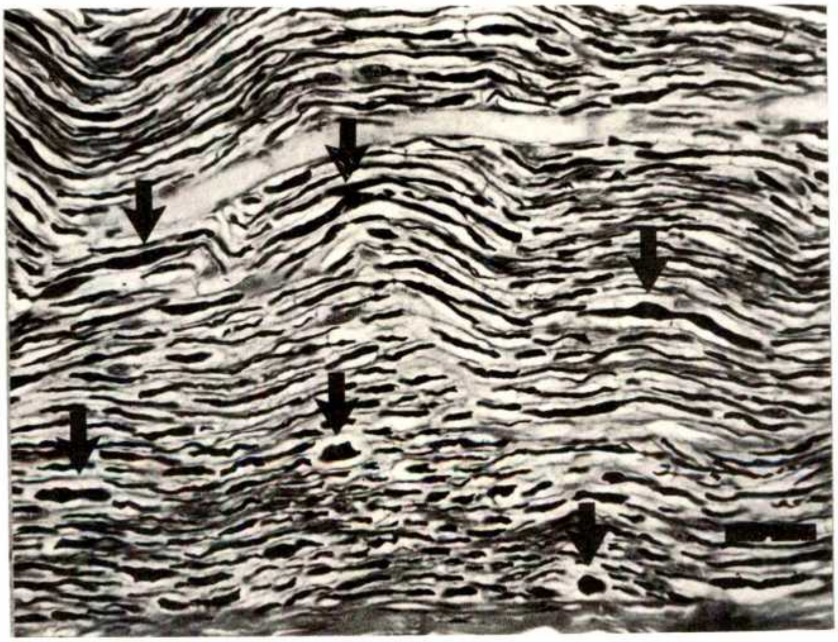

FIG. 11. Sciatic nerve. Several swollen axons visible (arrows). The majority are of normal size. Thirty-three days. Glees and Marsland. Bar = 40 μm.

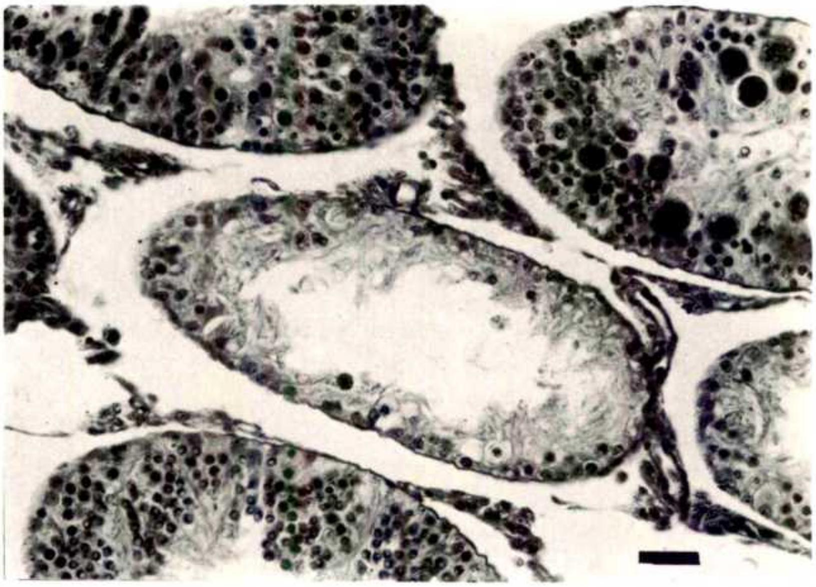

FIG. 12. Testis at thirty-three days. Note (*in centre*) a tubule with only surviving spermatogonia and Sertoli cells, and (*top right*) a tubule with many multinucleate spermatids. The latter arise from failure of the normal separation process. No spermatocytes in these or in those to left which are at slightly different stages of the cycle. Hæmatoxylin and eosin. Bar = 40 μm.

constant and early slowing of conduction velocity found in animals (Seppäläinen and Linnoila, 1975, 1976) and in man (Vasilescu, 1976) in chronic CS_2 intoxication, in which changes in nerves essentially similar to those described here have been found (Cavanagh *et al.*, 1978), this could well play an important role in the development of abnormal physical signs, rather than any irreversible degenerative changes in axons. The slowing of conduction velocity found in the study of Seppäläinen and Linnoila (1975, 1976) in CS_2 intoxication was certainly reversible, but we have yet to discover whether such events will also take place in animals severely intoxicated with 2,5 HDol.

Can any conclusions be drawn from this study about the underlying metabolic mechanisms leading to such widespread axonal swelling? It is known that the axonal swellings both in this condition and in CS_2 intoxication are expressions of intra-axonal accumulation of 10 nm neurofilaments of normal ultrastructural appearances, and that these displace the other intra-axonal organelles either to the periphery or into isolated clusters within the axon and the same occurs in chronic CS_2 intoxication. Other organelles also may increase in amount, such as smooth endoplasmic reticulum within axons, particularly near terminals, but these appear later, often when degenerative changes are already present in adjacent axons. It is difficult to ascribe any primary role to these latter structures since they do not occur in association with the early filamentous accumulations.

TABLE 2

Forebrain	Radial cortical fibres
	Corpus callosum
	Fornix
	Mammillary bodies
Brain-stem	Lateral lemniscus
	Ventral nuclei of thalamus
	Optic tracts
	Brachium of superior colliculi
	Lateral geniculate bodies
	Trapezoid body and its decussation
	Superior olives
	Spinocerebellar tracts
	Tectospinal tracts
	Reticular formation
	Transverse pontine fibres
	Pyramidal tracts at decussation
	Gracile nuclei
	Vestibular nuclei
	VIIIth nerve root
Cerebellum	White matter of folia
	Purkinje cell axons (torpedoes)
	Dentate and other roof nuclei
Spinal cord	Dorsal columns
	Pyramidal tracts
	Spinocerebellar tracts
	Probably tectospinal
	„ reticulospinal } in ventrolateral and
	„ vestibulospinal } ventromedial regions
	Middle root zones in lumbar regions
	Dorsomedial nuclei in dorsolumbar cord
	Anterior horns in lumbar region
	Dorsal spinal roots (lumbar)
Peripheral nerves	Oculomotor (in muscles)
	Hypoglossal (in tongue)
	Phrenic (in diaphragm)
	Vth and VIIth (in masseter)
	Sciatic
	Posterior tibial
	Terminals in tibialis anticus m.
	„ in gastrocnemius m.
	„ in suralis m.
	„ in foot muscles

Swollen axons were found in these CNS and PNS regions and pathways by staining with Glees and Marsland's technique after the twenty-fifth day of taking 2,5 hexanediol at 2 per cent and then 1 per cent in the drinking water.

Unfortunately, we know little yet about the importance of 10 nm neurofilaments to the life of the neuron and its processes. These macromolecular structures appear to be built up from three classes of polypeptides having molecular weights of 210,000, 155,000 and 70,000 daltons (Thorpe, Delacourte, Ayers, Bullock and Anderton, 1979). It is of considerable interest that abnormal accumulations of intra-axonal neurofilaments are also found in giant axonal neuropathy, a hereditary disease in man, which also occurs in the dog (Duncan and Griffiths, 1977, 1979) and the zebra (Higgins, Vandervelde, Hoff, Jagar, Cork and Silberman, 1977) and the pathological changes in these conditions closely resemble the changes in this intoxication. Perhaps one may tentatively conclude from this evidence alone that an enzyme defect may be responsible.

The functions of 10 nm neurofilaments in neurons is still uncertain but there is accumulating evidence that their degradation is effected by Ca^{++} activated proteases. Selective breakdown of neurofilament protein in rat nerve has been shown to occur in this way by Schlaepfer and Micko (1978), and in squid and *myxicola* axoplasm by Gilbert (1975), Gilbert, Newby and Anderton (1975) and by Anderton, Bell, Newby and Gilbert (1976). Recently this enzyme reaction has been further explored by Pant, Terakawa and Gainer (1979) and by Pant and Gainer (1980) in squid axoplasmic material and they have suggested that the enzyme, separable in the 100,000 × g supernatant, may selectively degrade only the 210,000 m.wt. protein, and is specifically activated by Ca^{++} ions but not by other divalent ionic species. Moreover, it is selectively inhibited by Cu^{++} and by Fe^{++} ions, and is sensitive to sulphydryl inhibitors, such as parachloromercuribenzoate and iodoacetic acid.

This last observation is of particular interest. It is now apparent (Krasavage, O'Donoghue, Di Vicenzo and Terhaar, 1980) that the proximate toxic substance produced by hexacarbon compounds in the tissues is almost certainly the diketone, 2,5 hexanedione, and that *n*-hexane, methylbutylketone, and 2,5 hexanediol (the dialcohol conversion product conveniently used in this experiment because of its water solubility) are all metabolized in the liver to this toxic product. As might be suspected from its chemical structure, the diketone interacts with -SH compounds (Sabri, Moore and Spencer, 1979) and shares this property with CS_2. This line of evidence would lead one to suspect that the Ca^{++} activated protease, likely in all probability to be responsible for the breakdown of neurofilaments along the length of the axon, could be specifically inhibited in hexacarbon and in chronic CS_2 intoxications. This may explain also why the accumulation of neurofibrils is predominantly, but not exclusively, towards the distal region of axons, and why fibre length does not appear to be crucial to its occurrence.

It is an interesting question as to why the accumulation seems to be predominantly but not exclusively distal in its distribution. Lasek and Hoffman (1976), who radioactively labelled the neurofilamentous protein, concluded that the breakdown was principally but not exclusively in the distal regions of the optic nerve fibres, and it seems probable therefore that, normally, degradation of filaments may be taking place along the length of the axons, but the intensity of which may vary at different distances along their length and probably also varying in intensity in different fibre pathways. At all events, it seems probable that at least some of the variations in the pattern of axonal involvement may find explanations along these lines. The condition, however, is not a primarily degenerative one, and is thus quite unlike the 'dying back' toxic neuropathies (Cavanagh, 1979).

SUMMARY

Using conventional selective staining of nervous tissue, we have followed the pattern of pathological changes by light microscopy in the nervous system of rats given 2 and 1 per cent 2,5 hexanediol dissolved in their drinking water over six weeks. Widespread enlargement of axons and of axon terminals were noted, which became visible after three to four weeks and were conspicuous from then onwards. The following systems were found affected: radial and other fibres in various parts of the cerebral cortex; corpus callosum; lower fornix and preterminals in the mammillary bodies; optic tracts, and the brachia of the superior colliculi, particularly in the stratum opticum, the lateral geniculate bodies, but very slightly in the optic chiasm and not in optic nerves; lateral lemniscus and preterminals in the ventral thalamus; spinal tracts, corticospinal tracts in medulla and throughout spinal cord; transverse fibres in the pons; the trapezoid body and its decussation, and the preterminals in the superior olives; the spinocerebellar tracts; fibres in the reticular formation; preterminals in the vestibular nuclei; VIIIth cranial nerves, and preterminals in the trigeminal nuclei and the gracile nuclei. In the cerebellum there were thickened fibres in the white matter of the vermis and elsewhere; thickening of mossy fibres and perhaps, too, of climbing fibres; torpedoes were not infrequently seen on the proximal parts of the Purkinje cell axons; and marked enlargement of fibres occurred in the spinocerebellar tracts. In the spinal cord, cervical levels showed marked swelling of fibres in the gracile tracts, in pyramidal tracts, in spinocerebellar and of other peripherally lying fibres in lateral and in ventral tracts.

In lumbosacral levels there was striking thickening of entering axons from dorsal roots in the middle root zones and passing into the grey matter; dorsomedial nuclei showed thickened fibres and preterminals, also present in intermediate zones and among anterior horn cells. Ventral roots were normal but lumbar dorsal roots showed many swollen fibres.

In peripheral nerves, swollen fibres were evident in muscles from foot, leg, diaphragm, tongue and face and in sciatic and posterior tibial nerves after thirty-two days. Degenerating nerve fibres were seen abundantly in the longer surviving animals in nerves to the posterior leg compartment, but were few and scanty before thirty-two days. No axon degeneration was seen up to fifty-eight days in CNS tracts except in dorsal columns and perhaps in the cerebellum; gliosis was minimal or absent. Chromatolysis was only seen in occasional lumbar dorsal root ganglia in longer surviving animals.

Accumulation of filaments within axons is thus a very widespread event from a relatively early stage of intoxication, associated neither with major functional disturbances nor with extensive degenerative changes except in a few peripheral nerves. The process is distinctive, but is similar to CS_2 intoxication and to certain apparently hereditary cases in man and in dogs. It is quite unlike other forms of systematized toxic neuropathy.

ACKNOWLEDGEMENT

We are grateful for a grant from Action Research for the Crippled Child which made this work possible.

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(*Received September 16, 1980*)

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REGIONAL CEREBRAL BLOOD FLOW DURING DEVELOPMENT AND AGEING OF THE RAT BRAIN

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INTRODUCTION

THE brain of the rat grows dramatically in the first four months of life, when regional morphological and neurochemical changes follow well-defined developmental time tables (Rosenberg and Stern, 1966; Dobbing, 1970; Timiras, 1972). Brain morphology and neurochemistry continue to change throughout life, particularly during senescence. After 12 months of age, for example, the density of dendritic spines in cortical pyramidal neurons declines, Purkinje cells in the cerebellum continue to die, neurotransmitter enzyme activities fall, and β-adrenergic receptors in the striatum and cerebellum decrease in number (Inukai, 1928; Feldman and Dowd, 1975; Feldman, 1976; McGeer, Fibiger, McGeer and Wickson, 1971; Weiss, Greenberg and Cantor, 1979).

After 3 weeks of age, the rat brain consumes glucose as the major substrate for oxidative metabolism (Siesjö, 1978). This makes it possible to examine cerebral functional activity in relation to cerebral metabolism by determining the rate of local cerebral glucose utilization (LCGU) (Sokoloff, Reivich, Kennedy, Des Rosiers, Patlak, Pettigrew, Sakurada and Shinohara, 1977). LCGU increases by an average of 20 per cent during the development period from 1 to 3 months of age in the Fischer-344 rat, which has a maximum lifespan of 36 months (Coleman, Barthold, Osbaldiston, Foster and Jonas, 1977), but declines significantly between 3 and 12 months of age (London, Nespor and Rapoport, 1980). In both the Fischer-344 and Sprague-Dawley rat, however, LCGU does not change significantly after 12 to 24 months of age (London *et al.*, 1980; Smith, Goochee, Rapoport and Sokoloff, 1980).

The constancy of resting LCGU after 12 months of age in the rat indicates that this parameter does not necessarily mirror the many morphological and neurochemical changes of senescence (*see above*). Furthermore it is not known why LCGU falls precipitously between 3 and 12 months of age in the rat, as cerebral functional activity is not reported to decline in this period. We therefore thought it important to employ another measure of cerebral functional activity, namely regional cerebral blood flow (rCBF), to examine the developing, mature and senescent rat brain.

It is well established that rCBF is regulated to meet the requirements of changing cerebral activity (Roy and Sherrington, 1890; Lassen, Ingvar and Skinhøj, 1978). Blood flow and glucose utilization are coupled in individual brain structures of conscious and anæsthetized rats under resting conditions and in response to increased or decreased functional demand (Reivich, 1974; reviewed by Sokoloff, 1978). Furthermore, over-all cerebral blood flow in the rat is correlated with the cerebral metabolic rate for oxygen ($CMRO_2$) during hypothermia, phenobarbitone anæsthesia, N_2O anæsthesia, hyperthermia, seizures and immobilization stress (reviewed by Nilsson, Rehncrona and Siesjö, 1978). A similar coupling between flow and $CMRO_2$ holds in normal human subjects and in subjects with chronic stable brain disease (Raichle, Grubb, Gado, Eichling and Ter-Pogossian, 1976).

In this paper, we present measurements of rCBF in the unanæsthetized, conscious Fischer-344 rat at each of 5 ages. Because these ages have been studied previously with the LCGU method (London *et al.*, 1980), we were able to examine the relation between rCBF and LCGU during development and ageing of the rat brain. An abstract of this work has been published (Ohata, Sundaram, Fredericks, London and Rapoport, 1980).

METHODS

Regional cerebral blood flow (rCBF) was measured in 14 specific regions of the brain of the Fischer-344 rat, by the methods of Sakurada, Kennedy, Jehle, Brown, Carbin and Sokoloff (1978) and Ohno, Pettigrew and Rapoport (1979). Twenty-one or 22 male rats were examined at either 1, 3, 12, 24 or 34 months of age. The animals were reared under barrier conditions by Charles River Breeding Laboratories (Wilmington, MA), and were allowed to adapt to the non-barrier environment of our laboratory for at least three days after their receipt. rCBF was determined within one week of the specified age of the 1-month-old animals, or within two weeks of the specified age of the others.

A rat was placed under light ether anæsthesia, and polyethylene catheters filled with 100 IU Na heparin per ml of 0.9 per cent (w/v) NaCl were tied through skin openings into the right femoral artery and vein. The skin was sutured at the catheter exit and infiltrated with 2 per cent butacaine sulphate (Abbott Laboratories, N. Chicago, IL). The hindquarters of the animal were wrapped in a cotton stocking and a fast-setting plaster bandage (Johnson and Johnson, New Brunswick, NJ), with hindlimbs and catheters protruding, and the bandage was lashed to a covered lead block. In the harness, the rat was able to move its forequarters freely and did not appear stressed.

The rat was allowed to recover from anæsthesia for 6 h or longer. Body core temperature was maintained at 36° C by placing a thermoprobe in the rectum, and connecting the probe to a feedback device (Indicating Controller Model 73A, Yellow Springs Instruments, Yellow Springs, OH) that activated heating wires on the roof of a chamber in which the animals were placed. The chamber was sound-insulated, but had one open side for access (London *et al.*, 1980).

After 6 h, the femoral vein catheter was connected to a 5 ml syringe which was held in a constant flow pump (Model 975, Harvard Apparatus Co., Millis, MA). A sample of arterial blood was removed from all but the 1-month old animals, for determination of P_aCO_2, P_aO_2 and plasma pH (pH-Blood Gas Analyzer No. 213, Instrumentation Laboratories, Lexington, MA). Immediately thereafter, the femoral vein was infused for 45 s at a rate of 1.1 ml.min^{-1}, with 0.9 per cent NaCl containing 10 μC.ml^{-1} of [^{14}C]-iodoantipyrine (New England Nuclear, Boston, MA; sp. act. = 50 mC.mmol^{-1}). Purity of [^{14}C]-iodoantipyrine was confirmed by thin layer chromatography (LK5D silica gel, Whatman Inc., Clifton, NJ) in a 7:3 (v/v) mixture of ethylacetate and benzene. Twenty μl samples of arterial blood were collected in heparinized tubes during infusion of tracer; 10 μl aliquots then were transferred to scintillation vials.

The rat was decapitated after 45 to 55 s of infusion. The skull was opened and the brain was removed and placed on filter paper wetted with cold 0.9 per cent NaCl. Large subarachnoidal and dural blood vessels were removed and discarded, after which grain regions were dissected out as described by Ohno *et al.* (1979), and weighed in tared scintillation vials. Vials that contained blood or brain samples received 1.5 ml of Soluene 350 (Packard Instruments Co., Downers Grove, IL) and were shaken for 6 h in a water bath at 60° C. Fifteen ml of Dimilume 30 (Packard), a liquid scintillation fluid, were added to brain and blood samples before counting of radioactivity by liquid scintillation spectroscopy (Model LS 9000 Liquid Scintillation Spectrometer, Beckman Instruments Co., Irvine, CA). Counts per minute (cpm) were converted to disintegrations per minute (dpm), by external standardization and predetermined efficiency curves.

Mathematical Analysis of Data

Rising arterial whole blood concentrations, C_{blood} dpm.ml^{-1}, which were measured during i.v. infusion of [^{14}C]-iodoantipyrine, were plotted against time and were fitted by a non-linear least-squares procedure with the following equation (Knott and Shrager, 1972; Ohno *et al.*, 1979), where A, B, D, R and S are constants,

$$C_{blood} = A + Be^{-Rt} + De^{-St} \tag{1}$$

In Equation 1, $A+B+D=0$ because $C_{blood}=0$ at $t=0$ (time when blood concentration starts to rise). The least-squares procedure provided best values for A, B, D, R and S in each experiment.

A transfer constant K can be defined as follows, where λ = steady-state, tissue: blood partition coefficient and m is a constant,

$$K = m(rCBF)/\lambda \tag{2}$$

K was obtained by least-squares fitting of the following equation to the measured brain concentration $C_{brain}(T)$, excluding intravascular tracer, at time T of decapitation,

$$\begin{aligned} C_{brain}(T)\lambda = {} & A-(A+BK/[K-R]+DK/[K-S])e^{-KT} \\ & +(K/[K-R])\,Be^{-RT}+(K/[K-S])De^{-ST} \end{aligned} \tag{3}$$

Intravascular radioactivity was calculated from regional cerebral blood volume and whole blood radioactivity at decapitation (Ohno *et al.*, 1979). K, which is the only unknown in Equation 3, was used to derive a value of rCBF by Equation 2, when letting $m = 1$ and $\lambda = 0.8$ for iodoantipyrine (Sakurada *et al.*, 1978). Statistical differences among mean values of rCBF or of other physiological parameters at different ages were determined at the $P = 0.05$ level by analysis of variance and Bonferroni t-statistics (Miller, 1966).

RESULTS

Table 1 lists mean values of physiological parameters that were measured in conscious Fischer-344 rats, aged 1, 3, 12, 24 and 34 months, just prior to the determination of rCBF by the i.v. infusion of [^{14}C]-iodoantipyrine. The results agree generally with those previously published (Rapoport, Ohno and Pettigrew, 1979; London *et al.*, 1980). Arterial pH did not change significantly with age, although P_aCO_2 and P_aO_2 rose to a significant extent between 3 and 24 months. Mean arterial blood pressure rose by 31 mmHg between 1 and 3 months, when it reached a maximal value, but was about 15 mmHg less than the 3 month value at 24 and 34 months of age ($P < 0.05$). Heart rate declined after 3 months, and was reduced significantly at 24 and 34 months. In the Fischer-344 rat, heart rate and mean arterial blood pressure fall with age despite a significant rise in plasma norepinephrine (Chiueh and Rapoport, 1979), possibly because the inotropic responsivity of the heart to catecholamines is diminished (Lakatta, Gerstenblith, Angell, Shock and Weisfeldt, 1975).

Table 2 summarizes mean values of rCBF in each of 14 brain regions, in rats aged 1, 3, 12, 24 and 34 months. The results agree generally with those previously published for mature, conscious rats (Sakurada *et al.*, 1978; Ohno *et al.*, 1979). Regions in the table are divided into three groups. Group I consists of grey matter regions from the forebrain, and the corpora quadrigemina (superior and inferior colliculi) from the midbrain. Group II consists of the remaining midbrain and regions from the hindbrain. Group III is white matter from the corpus callosum. Biochemical, anatomical and functional studies indicate that regions in Group II mature earlier during ontogeny than do those in Group I (Craigie, 1924; Himwich and Fazekas, 1941; Tyler and Van Harreveld, 1942; Zeman and Innes, 1963; Fox, 1964; H. E. Himwich, 1970; W. A. Himwich, 1973; Kennedy, Grave, Jehle and Sokoloff, 1972).

rCBF rose between 1 and 3 months in all of the brain regions that were examined (Table 2). The elevation averaged 32 per cent in the 9 Group I regions, and was

TABLE 1. MEAN PHYSIOLOGICAL PARAMETERS IN MALE FISCHER-344 RATS AT 5 DIFFERENT AGES

	Age (months)				
Parameter	*1*	*3*	*12*	*24*	*34*
No. of animals	21	22	22	21	22
Arterial pH	—	7.36±0.01*	7.38±0.01	7.34±0.02	7.33±0.02
P_aO_2, mmHg	—	82.5±2.4	90.3±2.8	93.9±3.6**	92.2±3.4
P_aCO_2, mmHg	—	36.3±0.8	38.6±1.3	41.6±1.8**	40.0±1.2
Mean arterial blood pressure, mmHg	91±3**	122±5	111±2†	105±5§,**	108±4**
Heart rate, beats/min	442±20	449±10	394±12†	343±20§**	332±16**
Body weight, g	81±3**	276±5	376±8**	416±9**	374±11**

*Mean ±SEM **Differs significantly from 3 month mean ($P < 0.05$). †18 animals. §15 animals. Bonferroni t-statistics (Miller, 1966) were used to compare means at 3 months with means at the other ages.

statistically significant in 8 of them ($P < 0.05$). For example, rCBF rose by 45 per cent in the olfactory bulb, by 46 per cent in the caudate nucleus, by 44 per cent in parietal grey matter, by 35 per cent in the hippocampus and by 34 per cent in the occipital lobe. The increase in rCBF in the 4 regions of Group II averaged only 10 per cent, and was not statistically significant in any of them.

rCBF tended to rise between 3 and 12 months of age in 8 of the 9 Group I regions from the forebrain and corpora quadrigemina (Table 2). However, the average increase was only 9 per cent, and the increase was significant only in the frontal lobe (+22 per cent). rCBF did not change significantly between 3 and 12 months in any of the 4 Group II regions. The average change equalled +3 per cent.

rCBF declined by an average of 17 per cent between 12 and 24 months of age in the 14 brain regions in Table 2. Statistically significant reductions occurred in the inferior colliculus (−30 per cent), thalamus+hypothalamus (−17 per cent), midbrain (−30 per cent), pons (−21 per cent) and medulla (−20 per cent). There were, however, no statistically significant changes in any of the regions between 24 and 34 months of age. During this last third of the life span (Coleman *et al.*, 1977), however, rCBF tended to rise by an average of 12 per cent in the 14 brain regions that were examined.

rCBF in white matter from the corpus callosum did not change significantly between 1 and 34 months of age, but rCBF in parietal grey matter rose by 85 per cent in this period, from 115 ml.100 g^{-1}.min^{-1} to 213 ml.100 g^{-1}.min^{-1}. The rise in grey but not white matter resulted in an age-related increase in the ratio, rCBF (grey)/rCBF (white), which equalled 2.8 at 1 month, 3.1 at 3 months, 4.1 at 12 months, 4.7 at 24 months and 4.5 at 34 months of age.

TABLE 2. rCBF AT 5 DIFFERENT AGES IN THE FISCHER-344 RAT

	Age (months)				
Brain Region	*1*	*3*	*12*	*24*	*34*
			rCBF, ml.100 g^{-1}.min^{-1}		
I. Forebrain + Corpora quadrigemina					
Olfactory bulb	77±5(21)*	112±4(22)**	121±7(22)	107±6(21)	121±7(22)
Frontal lobe	104±6	127±4	155±10**	141±8	149±7
Caudate nucleus	84±5	123±5**	115±8	97±7	105±5
Hippocampus	80±4	108±4**	118±7	103±6	117±6
Superior colliculus	85±6	105±4**	109±5	94±7	103±5
Inferior colliculus	99±6	118±5**	131±8	97±6**	115±6
Thalamus + hypothalamus	86±4	103±3**	117±6	97±6**	107±5
Occipital lobe	96±6	129±5**	136±8	119±7	131±7
Grey matter, parietal lobe	115±8	166±8**	188±11	179±15	213±18
II. Midbrain and hindbrain					
Midbrain	77±4	85±3	91±4	71±5**	80±4
Pons	79±4	86±3	89±4	70±4**	78±3
Cerebellum	72±4	82±3	80±4	65±4	70±4
Medulla	77±4	82±2	84±3	67±4**	74±3
III. White matter					
Corpus callosum	41±4	54±4	46±4	38±4	47±6

*Means ±SEM. (No. of animals). **Significantly changed ($P < 0.05$) as compared with mean rCBF at preceding age. Bonferroni t-statistics (Miller, 1966) were used to compare means between successive age groups.

DISCUSSION

In animals and man, rCBF reflects local neuronal functional activity. When neuronal activity is lowered by brain damage, sensory deprivation, thiopental anæsthesia or dementia, rCBF falls as well (Roy and Sherrington, 1890; Purves, 1972; Sokoloff, 1978; Lassen *et al.*, 1978; Siesjö, 1978; Nilsson *et al.*, 1978). Conversely, when neuronal activity increases, rCBF also rises. Thus, it is likely that the observed general rise in most Group I regions from the forebrain and corpora quadrigemina of the conscious rat, between 1 and 3 months of age, corresponds to an increased functional activity. This interpretation is consistent with an observed general increase in LCGU, another measure of functional activity, between 1 and 3 months (London *et al.*, 1980). Some of the elevation in rCBF during this period could be caused by the simultaneous rise in mean arterial blood pressure (Table 1), were cerebrovascular resistance to remain constant, but data on cerebrovascular resistance during development are unavailable.

The changes in rCBF between 1 and 3 months of age in the rat correspond to regional changes in cerebral capillary density (Craigie, 1924; Zeman and Innes, 1963). Most grey matter areas from the mid- and hindbrain attain maximum capillary density by 20 days of age, after which density remains constant or even declines. On the other hand, capillary density in cerebral cortical grey matter continues to increase throughout the first year of life. Because capillary density in white matter (for example, medial longitudinal bundle) may fall after 20 days, the density ratio between grey and white matter increases. A corresponding increase occurs for the flow ratio between grey and white matter (*see* text and Table 2). The dentate nucleus and granular and molecular layers of the cerebellum, which are phylogenetically newer than other parts of the cerebellum, continue to increase in capillary density during the first 4 months of life, after which density declines (Craigie, 1924; Zeman and Innes, 1963).

These studies of capillary density, as well as additional biochemical, morphological and functional studies, indicate that regions of the brain-stem generally mature earlier during ontogeny than do forebrain regions (Craigie, 1924; Tyler and Van Harreveld, 1942; Zeman and Innes, 1963; Fox, 1964; H. E. Himwich, 1970; W. A. Himwich, 1973; Kennedy *et al.*, 1972). *In vitro* O_2 utilization by the rat brain at birth is greatest in slices from the medulla and least in slices from the pallium, whereas the reverse is true at adulthood (Tyler and Van Harreveld, 1942). In the dog, rCBF in brain-stem nuclei is greater at birth and peaks earlier during development than in anterior brain regions (Kennedy *et al.*, 1972). In the corpora quadrigemina of the dog brain, however, rCBF peaks late in development, consistent with the late appearance of vision and hearing. Touch, pain and postural responses, which are mediated by the phylogenetically older posterior brain structures, appear early (Fox, 1964; Kennedy *et al.*, 1972).

In view of the ontogenic pattern of brain maturation, the large and usually statistically significant rise in rCBF in Group I brain regions between 1 and 3 months of age (Table 2, fig. 1) probably corresponds to the maturation of forebrain regions and corpora quadrigemina after 1 month of age (Zeman and Innes, 1963). Conversely, Group II regions may mature sufficiently by 1 month of age, so that later changes in rCBF are slight.

Biphasic time courses in rCBF that occur in the developing dog brain (Kennedy *et al.*, 1972) were not observed in the developing rat brain, possibly because 1 month was the earliest age that was examined. The dog brain reaches adult weight after 2 years as compared to 4 months for the rat brain (Himwich, 1973; Rosenberg and Stern, 1966). If developmental timetables are comparable between the rat and dog brain, then a brain age of 20 to 60 days in the dog is equivalent to about 10 days in the rat, when the rat brain begins to grow maximally (Craigie, 1924; Zeman and Innes, 1963; Dobbing, 1970).

rCBF has not been measured previously in the conscious rat in relation to development and ageing of the brain. However, net CBF has been measured at 20 days and 3 months of age in the barbiturate-anæsthetized rat, in which resting flow is much lower than in the conscious animal (Freygang and Sokoloff, 1958; Dahlquist and Persson, 1976). Between 20 days and 3 months of age in the anæsthetized rat, net CBF rises by 29 per cent, from 48 ml.100 g^{-1} to 62 ml.100 $g^{-1}.min^{-1}$. The change, however, is reported as statistically insignificant ($P > 0.05$) (Dahlquist and Persson, 1976).

Although rCBF and LCGU often can be related directly to brain functional activity (Roy and Sherrington, 1890; Purves, 1972; Reivich, 1974; Sokoloff, 1978; Lassen *et al.*, 1978), neither parameter clearly corresponds to the many complex events that occur during maturation and ageing of the rat brain (Swaiman, 1970; Himwich, 1970, 1973; Timiras, 1972; Benjamins and McKhann, 1976). Between 12 and 34 months of age when many senescent events occur in the rat brain (*see* Introduction), LCGU remains unchanged in most regions which have been examined (London *et al.*, 1980). Between 12 and 24 months of age, however, rCBF tends to fall, and statistically significant reductions are noted in 5 of the 14 regions in Table 2, 3 of which belong to the midbrain and hindbrain. rCBF tends to rise between 24 and 34 months of age, but in no region is the change statistically significant. If the rats with lower values of rCBF at 24 months of age died before 34 months, a tendency to rise after 24 months could reflect a survival effect (Schaie, 1977). Brain pathology is not notable in the 24- or 34-month-old Fischer-344 rat (Coleman *et al.*, 1977). However, a survival effect may explain why, in man, the incidence of brain pathology falls in the tenth decade of life (Peress, Kane and Aronson, 1973).

Reduced sensory input to the brain between 12 and 24 months of age, due to functional deafferentation, might account for the significant reduction of rCBF at the inferior colliculus (which is part of the central auditory pathway) and thalamus + hypothalamus regions (Table 2). Auditory deprivation in the rat reduces LCGU by 35 to 60 per cent in brain structures associated with audition (Sokoloff, 1977) and pyramidal cell dendritic spines are lessened in the auditory cortex of aged rats (Vaughan, 1977). There also is an age-related loss of retinal photoreceptors in pyramidal cell dendritic spines in the visual cortex of the Fischer-344 rat. The loss would be expected to be accompanied by a reduced LCGU in brain structures associated with vision (Feldman, 1976; Shinowara, Hoover, Rapoport and London, 1980). Unilateral enucleation in the rat is reported to reduce LCGU in structures from the contralateral brain (Kennedy, Des Rosiers, Jehle, Reivich, Sharp and Sokoloff, 1975; Sokoloff, 1977).

Coupling between rCBF and LCGU

LCGU and rCBF do not follow identical time courses during maturation and ageing of the brain of the Fischer-344 rat. LCGU increases as does rCBF between 1 and 3 months, but generally decreases between 3 and 12 months when rCBF remains

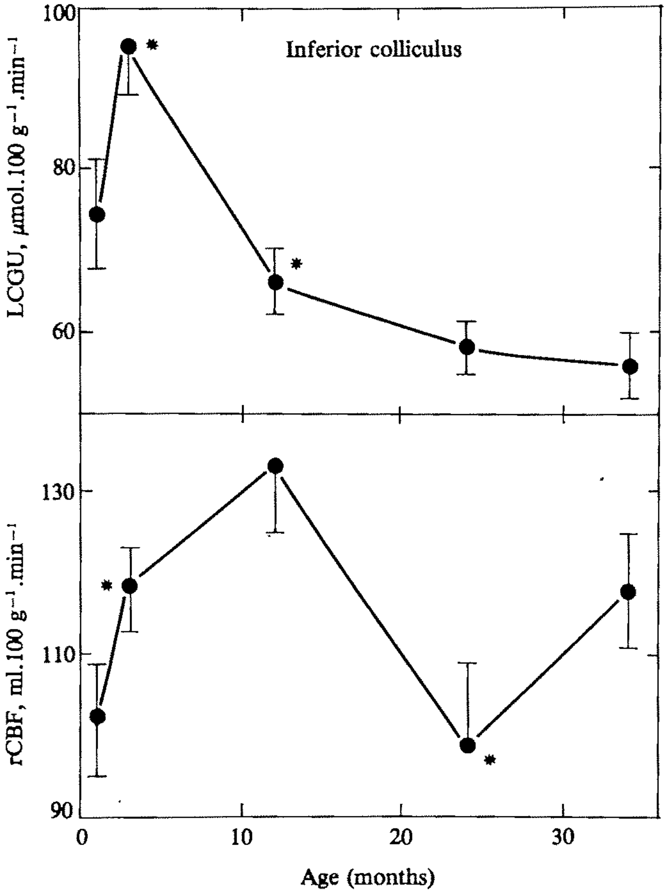

Fig. 1. Regional cerebral blood flow (rCBF) and local cerebral glucose utilization (LCGU) at the inferior colliculus, in relation to age of the Fischer-344 rat. Means ±SEM are shown. rCBF was taken from Table 2, whereas LCGU was taken from data by London *et al.* (1980 and unpublished observations). * = significantly different from earlier mean ($P < 0.05$) by Bonferroni t-statistics (Miller, 1966).

constant or tends to rise (London *et al.*, 1980). LCGU does not change significantly after 12 months of age, but rCBF falls significantly in 5 brain regions between 12 and 24 months (Table 2). The separate time courses of rCBF and LCGU in the inferior colliculus during development and ageing of the rat brain are illustrated in fig. 1.

Fig. 2 relates rCBF to LCGU (London *et al.*, 1980) in 12 regions of the brain of the Fischer-344 rat, at each of 5 ages. The linear least-squares fit to the data at each age is given by the following equation:

$$\text{rCBF} = m\,\text{LCGU} + b \tag{4}$$

where m is the slope that relates the incremental change in rCBF to that in LCGU, and b is the intercept at LCGU = 0. The slope m, in units of ml(blood) per μmol(glucose), equals 0.68 ± 0.16 (SE) at 1 month of age, 1.12 ± 0.20 at 3 months, 2.00 ± 0.34 at 12 months, 2.01 ± 0.33 at 24 months and 2.03 ± 0.33 at 34 months. It

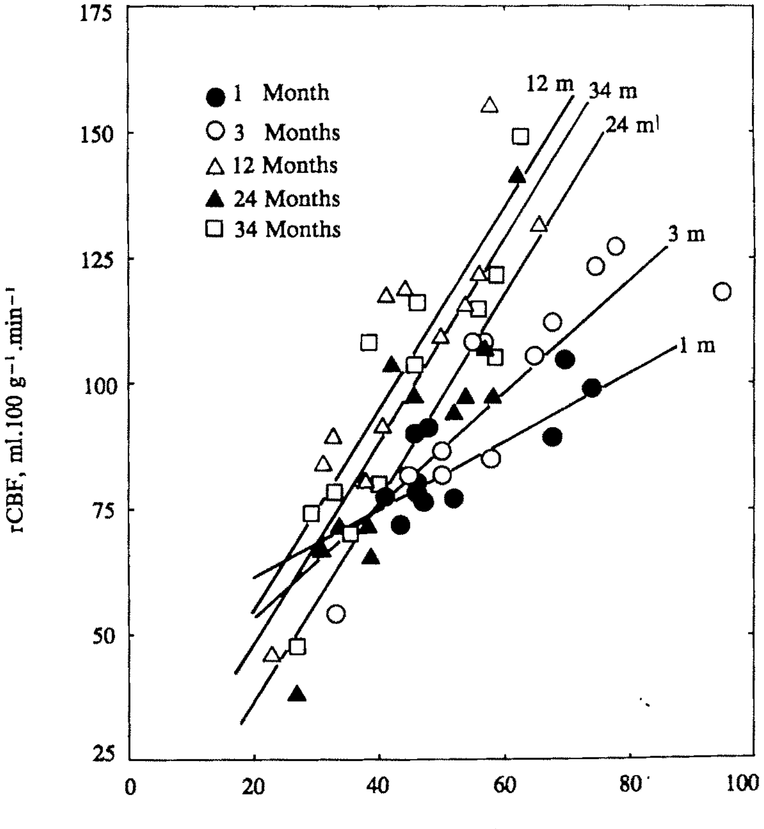

Fig. 2. Relation of mean regional cerebral blood flow (rCBF) at each of 12 brain regions to mean local cerebral glucose utilization (LCGU) at 5 different ages of the unanæsthetized Fischer-344 rat. rCBF is taken from Table 2, LCGU from London *et al.* (1980 and unpublished observations). Regression lines, for which slopes *m* are given in text, were obtained by linear least squares fitting of Equation 4 to the data from each age group.

increases significantly ($P < 0.05$ between 1 and 12 months. At 3 months of age, *m* approximates the slope reported for conscious, mature Sprague-Dawley rats (Des Rosiers, in Sokoloff, 1978).

The relations between rCBF and LCGU that are illustrated in fig. 2 do not establish, however, a functional dependence of rCBF on LCGU. rCBF is coupled directly to cerebral oxidative metabolism, as measured by $CMRO_2$ (Nilsson *et al.*, 1978; Sokoloff, 1978; Siesjö, 1978; Silver, 1978), and not to cerebral glucose utilization. If the ratio of $CMRO_2$ to LCGU were to change with age, as it does during starvation, following weaning, during hypoxia and hypercapnia in the rat (Cohen, Alexander, Smith, Reivich and Wollman, 1967; Owen, Morgan, Kemp, Sullivan, Herrera and Cahill, 1967; Dahlquist and Persson, 1976; Siesjö, 1978), then the correlation between rCBF and LCGU could change even if coupling remained constant between rCBF and oxidative metabolism (as measured by $CMRO_2$).

There is no evidence, however, that the ratio of O_2 utilization to glucose utilization changes between the ages of 3 and 12 months in the rat, when rCBF remains constant or tends to rise, and LCGU falls (*see* fig. 2). Such a change might reflect an increased contribution of ketone bodies to brain oxidative metabolism between 3 and 12 months, but it is likely that ketone body utilization is minimal and at the adult level by 3 months of age (Hawkins, Williamson and Krebs, 1971; Dahlquist and Persson, 1976). Enzymes that mediate ketone body metabolism certainly have adult activities by 3 months (Klee and Sokoloff, 1967; Tildon, Cone and Cornblath, 1971; Williamson, Bates, Page and Krebs, 1971; Middleton, 1973).

A change in the O_2/glucose utilization ratio might occur after 3 months of age if the hexose monophosphate shunt, which diverts glucose moities to the nucleic acids of RNA and DNA, were more active at 3 than at 12 months. However, the shunt is probably at the adult level by 2 months, when brain RNA and DNA and the $NADPH/NADP^+$ ratio (an indirect measure of shunt activity) are at adult levels (Guarneri and Bonavita, 1966; Ford, 1973; Benjamins and McKhann, 1976; Siesjö, 1978). Furthermore, glucose that is consumed by the rat brain at 3 months is almost entirely oxidized or converted to lactate and pyruvate (Hawkins *et al.*, 1971; Dahlquist and Persson, 1976; Siesjö, 1978).

We therefore suggest that the separate time-courses of rCBF and LCGU between 3 and 12 months of age reflect a resetting of the functional coupling relation between rCBF and brain oxidative metabolism. Because rCBF tends to increase or remain unchanged when LCGU falls significantly between 3 and 12 months of age, the slope *m* (Equation 4), which relates both parameters at different regions, is greater at 12 than at 3 months. An increased slope suggests that the control mechanism that determines rCBF in relation to oxidative metabolism is more sensitive at 12 months than at 3 months to a specific product or substrate of metabolism (Purves, 1972; Raichle *et al.*, 1976; Silver, 1978; Nilsson *et al.*, 1978; Siesjö, 1978). Maturation of neurogenic control of rCBF (Edvinsson and MacKenzie, 1977) conceivably could influence the coupling relation between rCBF and oxidative metabolism.

SUMMARY

Regional cerebral blood flow (rCBF) in the conscious Fischer-344 rat was measured in 14 brain regions at 5 different ages. rCBF increased significantly ($P < 0.05$) in most anterior brain regions between 1 and 3 months of age, but not in phylogenetically more primitive regions from the mid- and hindbrain that may have matured prior to 1 month of age. rCBF tended to increase or remain constant between 3 and 12 months, and rose significantly in the frontal lobe. Between 12 and 24 months of age, rCBF declined by an average of 17 per cent and fell significantly in 5 brain regions, mainly from the posterior brain, and in some, possibly in relation to partial functional deafferentation. There were no statistically significant changes in rCBF between 24 and 34 months of age. rCBF and local cerebral glucose utilization (LCGU) do not follow identical time courses during development and maturation of the rat brain. A fall in LCGU between 3 and 12 months of age, when rCBF remains constant or tends to rise, may reflect increased sensitivity of the cerebrovascular bed to metabolic factors which regulate cerebral blood flow.

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(*Received October 9, 1980*)

Brain (1981), **104**, 333-350

CONTRAST SENSITIVITY, VISUAL ACUITY AND THE DISCRIMINATION OF SNELLEN LETTERS IN MULTIPLE SCLEROSIS[1]

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INTRODUCTION

WE reported previously that a considerable proportion (20/48) of patients with multiple sclerosis showed contrast sensitivity losses that could not be detected by visual acuity measures such as cut-off spatial frequency or the Snellen test, and this observation has been confirmed in other laboratories (Regan, Silver and Murray, 1977; Ginsburg, 1978, 1981; Zimmern, Campbell and Wilkinson, 1979). (Note that disordered contrast sensitivity is not peculiar to multiple sclerosis; it can also result from damage to visual cortex (Bodis-Wollner, 1972), glaucoma (Arden and Jacobson, 1978) and from amblyopia (Ginsburg, 1978; Hess, Howell and Kitchen, 1978).) If it can be assumed that test results obtained with the sinewave gratings used in all the above studies predict visual sensitivity to everyday objects, then a patient with depressed contrast sensitivity but normal Snellen acuity might experience difficulty in seeing even large objects (such as automobiles) in conditions of hazy or foggy visibility, although his ability to read the smallest high-contrast print was unimpaired.

We found that in some patients, the depression of contrast sensitivity was restricted to a comparatively narrow band of middle spatial frequencies, high spatial frequencies and low spatial frequencies being spared. On the basis of Blakemore and Campbell's (1969) proposal that shape is defined by the relative amplitudes of different spatial frequency components Regan *et al.* (1977) suggested that one consequence of such a 'medium frequency' loss of contrast sensitivity might be impairment of the patient's ability to recognize an object's shape independently of its magnification. Such a defect of shape or object recognition might masquerade as a cognitive disorder, though in reality it was a predictable consequence of comparatively peripheral pathology.

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[1] This work was presented to the Canadian Congress of Neurological Sciences, Halifax, 1979 (Regan, Raymond, Ginsburg and Murray, 1979).

Fig. 1 illustrates the rationale of this prediction. Panels A, B and C show a plot of sinewave contrast sensitivity typical of control subjects. The normal plot is fairly smooth with a broad peak of sensitivity at about 5 cycles/degree. Panels D to I in fig. 1 illustrate an (idealized) plot for a patient with the 'medium frequency' loss of sensitivity described previously. Suppose that, of the wide range of spatial frequencies associated with an object of given shape, only a comparatively narrow range is important for recognizing the shape (Ginsburg, 1971). In figs. 1A to F we suppose that this important range of spatial frequencies is not much wider than the notch in the contrast sensitivity curve. Figs. 1A to C illustrate how this important

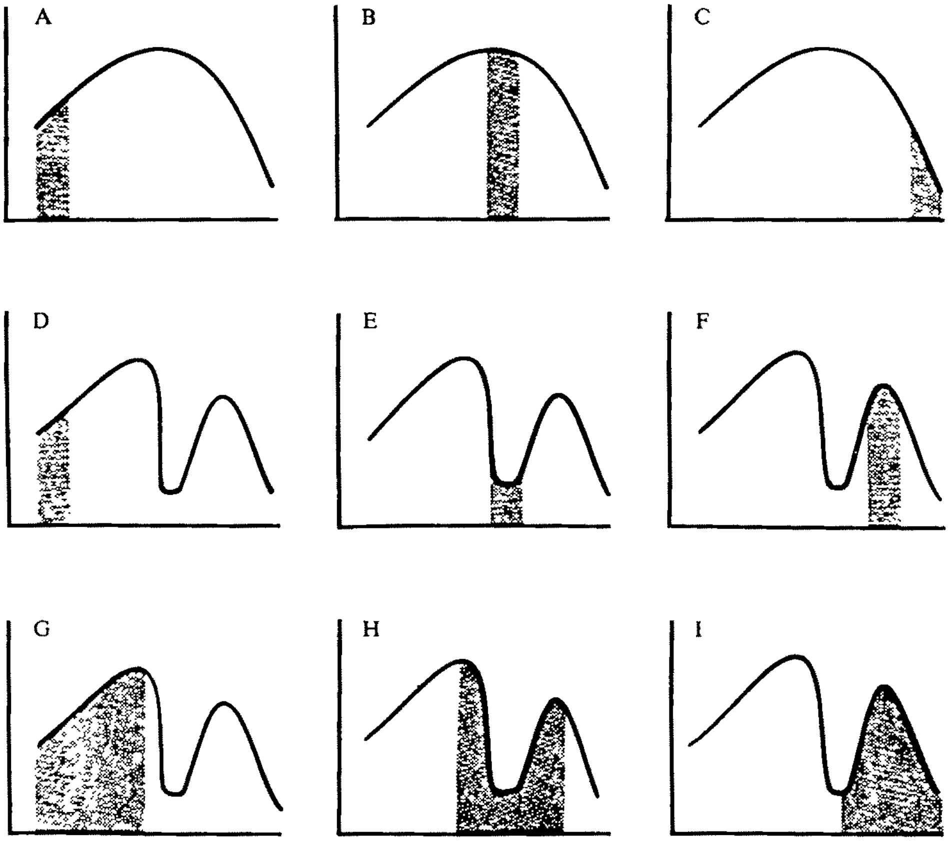


FIG. 1. Detecting versus discriminating a shape. Panels A–I are sinewave contrast sensitivity curves with contrast thresholds plotted as ordinates *versus* spatial frequency as abscissæ. Panels A–C show contrast sensitivity curves typical of control subjects. The shaded region is supposed to represent the range of spatial frequencies which is important for recognizing a letter. This region moves along the curve in A–C as the subject moves away from the target. Panels D–I show data representative of a patient with multiple sclerosis with a 'medium-frequency notch'. In D–F only a narrow range of spatial frequencies is supposed to be important for recognizing a letter, while in G–I a wide range of spatial frequencies is supposed to be important for recognizing a letter.

range of spatial frequencies moves along a control subject's contrast sensitivity curve as the subject progressively moves further away from the shape (for example, letter 'C'). Even a low contrast 'C' would be recognized when the relevant spatial frequency band was centred at about or somewhat below 5 cycles/degree as in fig. 1B, but as the viewing distance increased, higher and higher contrasts would be required to allow the 'C' to be recognized, until the subject's contrast sensitivity for the spatial frequencies important for recognition was so low that he would fail to recognize a 'C' of even the highest contrast.

Now we consider the prediction for a patient. At close viewing distances the patient's ability to recognize the 'C' would be similar to control subjects' (compare figs. 1D and 1A). At a somewhat greater viewing distance, the spatial frequencies important for recognition would be just those frequencies for which the patient had lower contrast sensitivity (fig. 1E), so that only a high-contrast 'C' would be recognized. However, if the patient increased the viewing distance still further (fig. 1F) he would once again have normal sensitivity to the spatial frequencies important for recognition, so that he would once again recognize even a low contrast 'C'. Clearly, this minimum in discrimination would not be predictable on the basis of visual acuity or cut-off spatial frequency.

Figs. 1G–I illustrate the case that the width of the spatial frequency band important for recognition is much wider than the medium frequency notch in the patient's contrast sensitivity curve. In this situation, the dip in recognition caused by the notch would be appreciably less evident than when the important spatial frequency band was narrow as in figs. 1D–F.

In this paper we investigate whether visual test results obtained with sinewave gratings accurately predict results obtained with more complex test targets. In particular, we compare a subject's ability to *detect* sinewave gratings (that contain only one spatial frequency) with his or her ability to *discriminate* between targets that contain many spatial frequencies, namely, Snellen letters.

METHODS

Apparatus

Sinewave grating contrast sensitivity curves were measured by means of grating stimuli displayed on the face of a Tektronix type 604 CRT with type 31 phosphor. The gratings were generated conventionally (Schade, 1956; Campbell and Robson, 1968). Subjects fixated on the centre of a circular stimulus field whose diameter was 9.5 cm (3.2 deg visual angle), and whose mean luminance was 29 cd/m^2. The stimulus field was surrounded by an adapting field of mean luminance 545 cd/m^2 that extended to a diameter of 10 deg. The viewing distance was 171 cm. The purpose of the large photopic adapting field was to firmly hold the eye's state of adaptation at a sufficiently high photopic level so that visual acuity and the dynamic properties of the eye were constant and unaffected by changes in stimulus luminance. We therefore used a large surround with a retinal illumination as close as we could arrange to the 5000 photopic trolands required to eliminate the rod influence (Aguilar and Stiles, 1954).

Letter discrimination was measured using the projection system shown in fig. 2. Letters were back-projected from Kodak 'Carousel' projectors on to a screen measuring 2.5 cm horizontally by 2.2 cm vertically. The projection screen was surrounded by an adapting screen illuminated by white light to a level of 18 cd/m^2. Subjects viewed the projection screen from several distances between 145 cm and 1000 cm. The beams from the two slide projectors passed through a green Wratten filter (No. 74) in order to minimize any colour differences between the projector lights. Projector No. 1 contained one letter and projector No. 2 contained the other letter. The relative intensities of the letters were controlled by neutral density filters (ND1 and ND2) and the intensity of the letters was controlled together by neutral density filter ND3. In preliminary experiments a third projector (not shown) provided background illumination so that letter contrast could be varied over a wide range. In the experiments reported below the third projector was not used. The timing of letter presentations was electronically controlled by Uniblitz shutters. The duration of the projected letters was selected as follows: it is known that contrast thresholds fall as presentation duration is increased. This reduction of threshold extends to about 60 ms at a spatial frequency of 0.5 cycles/deg and to about 200 ms at about 16 cycles/deg (Breitmeyer and Ganz, 1977). The shape of the contrast sensitivity curve is approximately

A

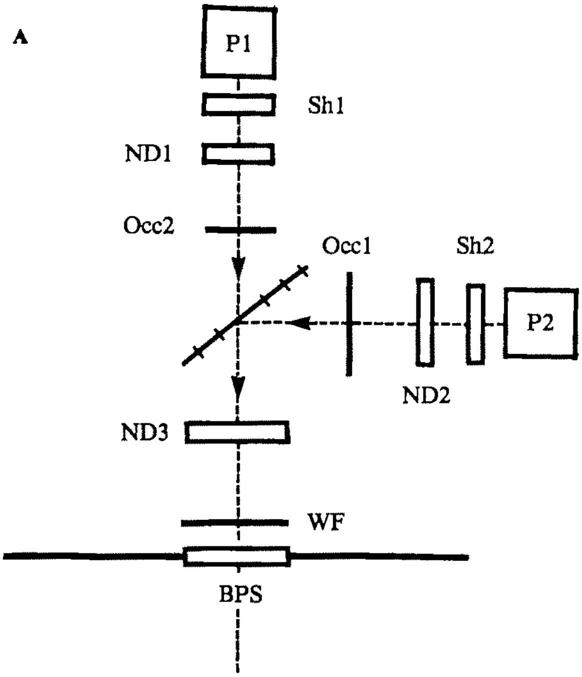
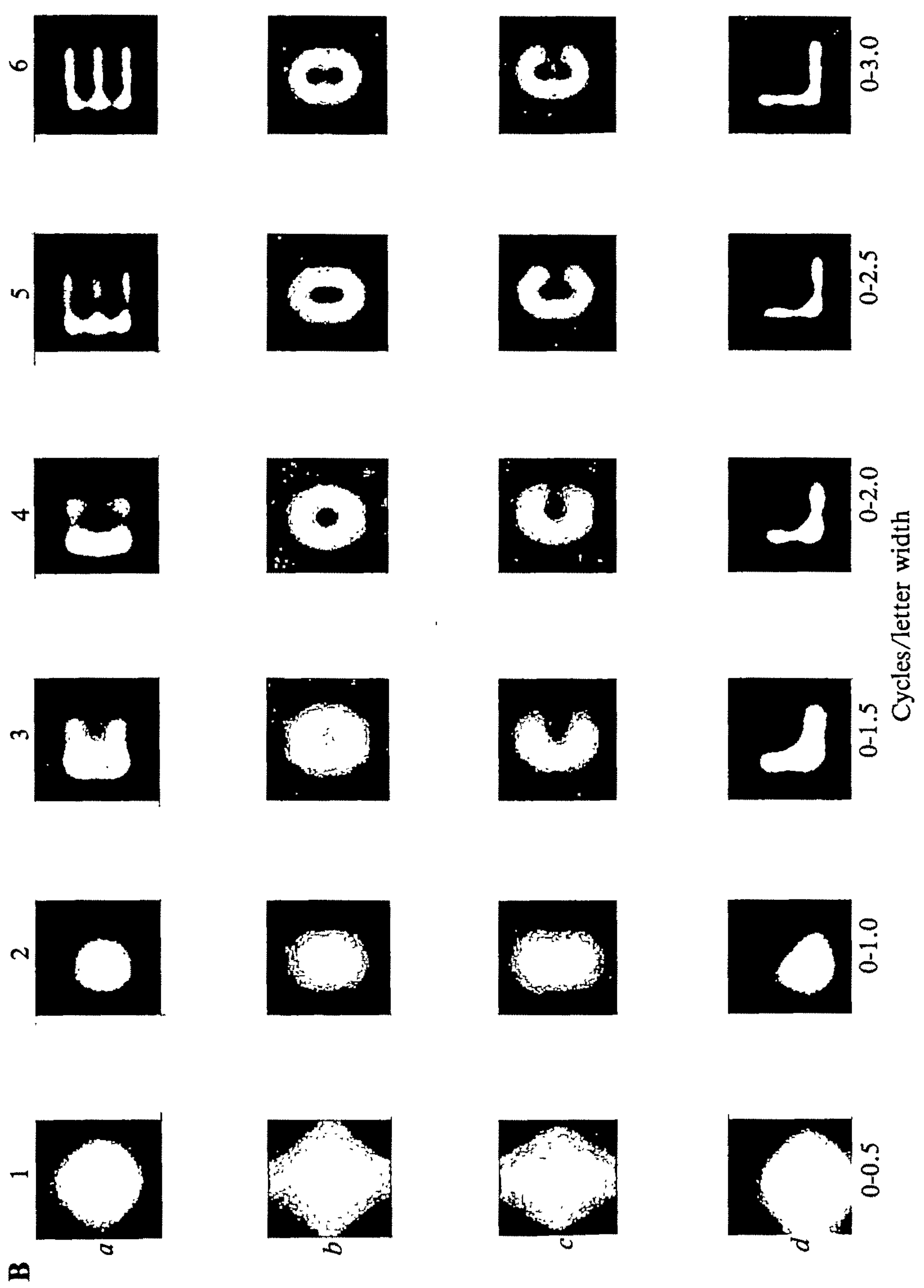


FIG. 2A, visual stimulation apparatus. P1, P2 = projectors; Sh1, Sh2 = electronically-controlled shutters; ND1, ND2, ND3 = neutral density filters; Occ1, Occ2 = occluders; WF = green Wratten filters; BPS = back projection screen.

FIG. 2B (*opposite*), spatially-filtered test letters. The letters E, O, C and L (rows A–D) were synthesized by two-dimensional Fourier techniques in steps of 0.5 cycles/letter width (columns 1–6) in order to determine the minimum range of spatial frequencies necessary for their correct recognition. The figure shows that a spatial frequency range up to 2.5 cycles/letter width is required for correct recognition of the letter 'E' while the spatial frequency range up to only 1.5 cycles/letter width is adequate for correct recognition of the letter 'L' or 'O'.

The letters used in this study were 'E's containing spatial frequencies up to 2.0 and 2.5 cycles/letter width (4*a* and 5*a*, respectively) and an 'O' and 'C' both containing spatial frequencies up to 2.5 cycles/letter width (5*b* and *c*, respectively).


B
a
b
c
d
1
2
3
4
5
6
0-0.5
0-1.0
0-1.5
0-2.0
0-2.5
0-3.0
Cycles/letter width

the same for a 200-ms presentation as for continuous viewing (Kitterle and Rysberg, 1976; Kitterle and Corwin, 1979). We therefore chose our duration of letter presentation to be not less than 200 ms. On the other hand, the presentation should be sufficiently brief to ensure that no eye movements occurring during the presentation could be triggered by the presentation. Since the latency of an eye movement is about 200 ms we selected 200 ms as the duration of letter presentations. Letters were presented with an interval of 1 s between the two flashes.

Immediately below the projection screen was a 9 × 5.7-cm aperture behind which was a CRT (Telequipment type D83 with a green phosphor type P31). High-contrast (94 per cent) square-wave gratings, generated on the CRT by conventional means, were used to measure visual acuity at different viewing distances.

Filtered Letters

High contrast letters were synthesized by two-dimensional Fourier techniques. They were defined analytically for a 64 × 64 picture element (pel) matrix on a 128 × 128 pel grid having two intensity levels, black and white. The digitized letters were spatially filtered and photographed as described previously (Ginsburg, 1978).

Note that it is important to distinguish between the two descriptions of the spatial frequency content of a letter, namely, when expressed in cycles/letter width and when expressed in cycles/deg. The spatial frequencies are, of course, the same but the expression in terms of cycles/width is independent of viewing distance and so emphasizes the spatial information contained in a particular letter, whereas cycles/deg depend on viewing distance. Thus, Ginsburg (1978, 1981) does not need to specify viewing distance in his proposal that 'Snellen letter recognition can be achieved on the basis of spatial frequencies in the range 1.5 to 2.5 cycles/width' (in other words, that this range contains minimal shape information for recognition).

Psychophysical Methods

Letter discrimination was measured by a two-alternative forced choice method. The subject initiated a sequence by pressing a 'start' button. After a 500-ms delay, the two letters were presented. The sequence of letters in each pair was randomized. The subject then pressed a button marked 'first' or 'second'. Subjects were instructed to judge which of a letter pair had been presented first, and if uncertain, to make a best guess. For example, with an 'O/C' pair, the subject would press the 'first' button if the 'O' came before the 'C'. At the start of each experimental session several practice runs were carried out at a short viewing distance where the subject could easily discriminate the letters.

Grating contrast sensitivity curves were measured using the method of limits with four ascending and four descending sequences per measurement. The order of spatial frequencies tested was randomized, and left and right eyes were tested alternately. Eight measurements of contrast threshold were averaged for each point in all experiments such as that shown in fig. 3. Every experiment carried out by a patient or by a control subject was repeated at least once on a different day and on at least two subjects.

In some preliminary experiments to test the effect of letter size on letter discrimination we varied the contrast of the letter pair over a wide range, and in other preliminary experiments we kept letter contrast at the highest level attainable and varied the intensity of the letter pair (in any pair the two letters were always of equal intensities and contrasts). In these experiments we measured percentage correct discrimination for each of several values of neutral density filter ND3 in fig. 2. We then plotted percentage correct discrimination on a probability axis *versus* density (in log units) plotted on a linear axis, fitted a linear regression line, and expressed discrimination as the neutral density for 80 per cent correct discrimination. Each percentage correct discrimination was based on 16 trials. The viewing distances and use of the left or right eye was randomized. Patients 1, 5, 6 and 7 carried out this experiment for discrimination between an 'E' filtered up to 2.0 cycles/width and an 'E' filtered up to 2.5 cycles/width. Patients 1 and 7 carried out this experiment for filtered 'O/C' discrimination. Three control subjects carried out this experiment for 'E/E' discrimination.

Our main experimental study was carried out by a different method. In order to test the effect of letter size on letter discrimination we held the letter intensity at a constant level, and measured percentage correct discriminations for different viewing distances. In these experiments we based percentage correct values on 40 trials per point. Viewing distances and the eye used were randomized, and we recorded only 10 trials before changing viewing distance or eye used. Patients 1 and 3 carried out this experiment for 'E/E' discrimination and Patients 1, 2, 3, 4, 6 and 7 carried out this experiment for unfiltered 'O/C' and for filtered 'O/C' discriminations. Three control subjects carried out this experiment for 'E/E' discrimination, and 8 control subjects carried out this experiment for filtered 'O/C' discrimination and for unfiltered 'O/C' discrimination. Patient 1 carried out an experiment at a fixed viewing distance in which we measured percentage correct discrimination between an unfiltered 'O' and the filtered 'O' used above. The relative intensities of the 'O's were varied in steps of 0·1 log unit from the filtered 'O', 0.4 log unit brighter to 0·4 log unit dimmer than the unfiltered 'O'. Different values of relative intensity were presented in random order. Each percentage correct value was based on 40 trials, and all 40 trials were presented in a block.

The contrast of the letters was determined by using a photomultiplier to measure the intensity of the light passing through their darkest and brightest parts. The ratio between the light intensities transmitted through the darkest and the brightest region was 0.38 for the filtered 'O' and 'C', 0.25 for the unfiltered 'O' and 'C' and 0.1 for the three filtered 'E's. These estimates of letter contrast are only rough estimates since the sampling aperture in front of the photomultiplier was relatively large as compared to the size of the filtered letters. (The sampling aperture was a 1 cm × 1 cm square and the filtered letters were magnified to 15 cm high × 12.7 cm wide.)

Visual acuity using high-contrast square-wave gratings was measured by the method of limits. Each measurement was the mean of three ascending and three descending series of spatial frequencies.

Control Subjects and Patients

Control subjects comprised 4 males and 5 females whose ages ranged from 17 to 33 years. Snellen acuities, measured with refractive correction where necessary, were 20/30 or better for all subjects. All controls were paid volunteers. Informed consent was obtained from all patients and control subjects.

Patients comprised 7 females whose ages ranged from 21 to 53 years. All were diagnosed 'definite' multiple sclerosis (Schumacher, Beebe and Kilber, 1968; Rose, Ellison, Myers and Tourtelotte, 1976). Clinical histories and the Kurtzke (1965) classifications are summarized in Table 1. The patients studied here were selected from a substantial number of greater than 100 multiple sclerosis patients whose contrast sensitivity curves we had previously measured. Our criteria for selection were as follows: (*a*) the presence of a 'medium frequency' loss or 'low frequency' loss in one eye's contrast sensitivity curve (more than 2:1 loss) with the other eye normal, and both eyes better than 20/30 Snellen acuity; (*b*) motor and bladder problems not to be so severe that the tests would be an unpleasant experience; (*c*) the patient's domicile to be in or near the testing location; (*d*) patients to be willing to attend several sessions.

TABLE 1. CLINICAL DATA ON PATIENTS DIAGNOSED AS DEFINITE MULTIPLE SCLEROSIS

Patient	*Age (yrs)*	*Sex*	*Onset*	*Kurtzke scale*	*Eye signs*	*Snellen Acuity*	
						L	*R*
1	44	F	1966	3	Internuclear ophthalmoplegia (R); vertical nystagmus, pale discs	20/30	20/30
2	36	F	1976	1	None	20/30	20/30
3	31	F	1973	1	None	20/20	20/20
4	28	F	1974	1	Bilateral internuclear ophthalmoplegia	20/30	20/30
5	31	F	1968	2	None	20/30	20/30
6	53	F	1959	3	None	20/30	20/30
7	21	F	1975	1	None	20/15	20/20

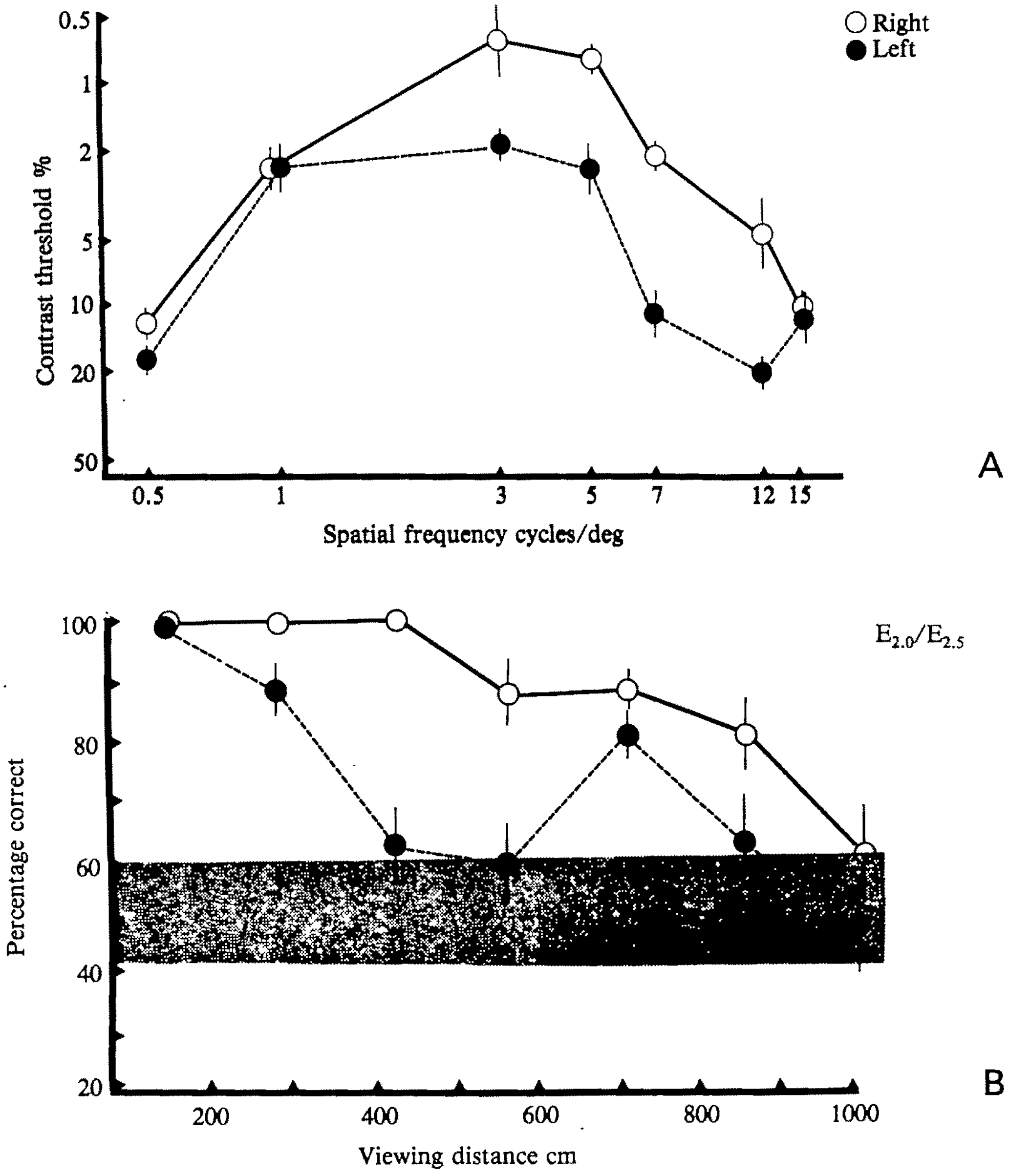
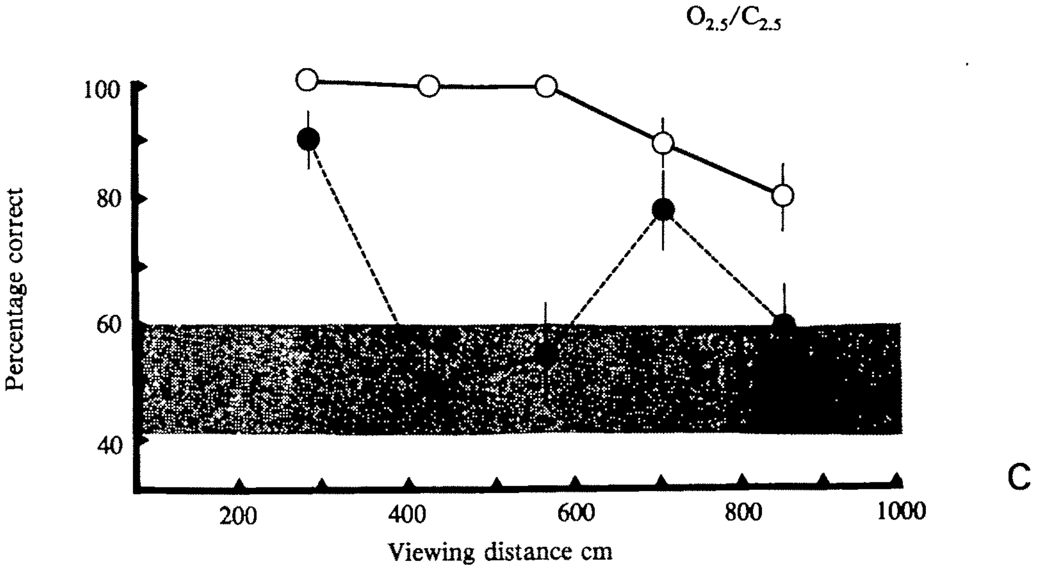
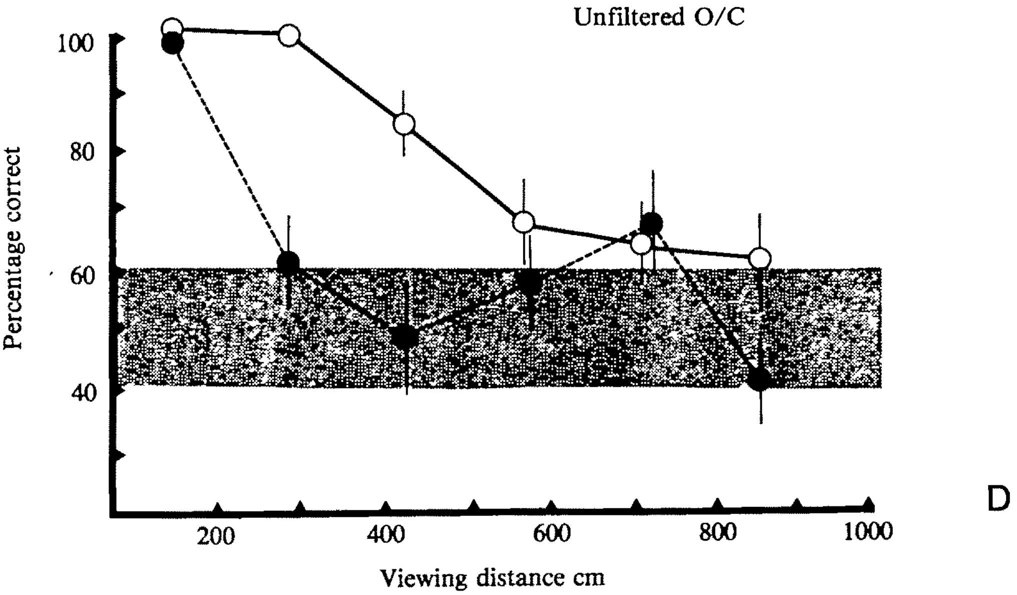


FIG. 3. Data for a multiple sclerosis patient. A, sinewave contrast sensitivity curve for Patient 1 showing 'notch' at medium spatial frequencies. B, percentage correct discriminations between two spatially-filtered 'E's for different viewing distances. The failure in discrimination for viewing distances near 400 to 500 cm corresponded to the notch in the left eye's contrast sensitivity curve in A. One 'E' was filtered up to 2.0 and the other to 2.5 cycles/letter width as illustrated in fig. 2B. C, percentage correct discriminations between a spatially-filtered 'O' and a spatially-filtered 'C' for different viewing distances. The failure in discrimination for viewing distances near 400 to 600 cm corresponded to the notch in the left eye's contrast sensitivity curve in A. Both letters were filtered up to 2.5 cycles/letter width and are illustrated in fig. 2B. D, percentage correct discrimination between an unfiltered (sharp) 'O' and an unfiltered 'C' for different viewing distances. Note the failure of discrimination for viewing distances near 300 to 600 cm.


$O_{2.5}/C_{2.5}$
100
80
60
40
Percentage correct
200
400
600
800
1000
Viewing distance cm
C


Unfiltered O/C
100
80
60
40
Percentage correct
200
400
600
800
1000
Viewing distance cm
D

RESULTS

Variation of Visual Acuity with Viewing Distance

Visual acuity (that is, cut-off spatial frequency) for the high-contrast grating target did not vary with viewing distance sufficiently to affect our conclusions for any control subject or for any patient. At a viewing distance of 20 feet, Snellen acuity was the same in the left and right eyes for all except one patient and one control subject, and was 20/30 or better in every case.

Sinewave Grating Contrast Sensitivity Curves

With the exception of Control Subject 9 (*see below*) sinewave grating contrast sensitivity curves for control subjects resembled those we have previously recorded for psychophysically-inexperienced subjects (Regan *et al.*, 1977; Regan, Whitlock, Murray and Beverley, 1980; Ginsburg, 1978). They approximated smooth curves with a broad peak near 5 cycles/deg. These plots differ slightly from plots recorded with practised subjects in that inexperienced subjects have a tendency to record somewhat higher threshold at high spatial frequencies, perhaps because, as previously noted, a high spatial frequency grating at threshold looks rather different to what some inexperienced subjects expect (Campbell and Robson, 1968). The range of inter-subject variation in contrast sensitivity at 5 cycles/deg for control subjects with 20/20 Snellen acuity was about ±2:1. On the basis of both the present study and our previous studies of contrast sensitivity in control subjects we took a difference of greater than 2:1 between the contrast sensitivities of the left and right eyes as abnormal in those subjects who had similar cut-off spatial frequencies and Snellen acuities in the left and right eyes. Except for Subject 9, no control subject had a significant difference between grating sensitivities for the left and right eyes near 5 cycles/deg. One control subject (No. 9) had a marginally significant dip (7 dB) in the contrast sensitivity curve of his left eye relative to his right eye in the range 5 to 13 cycles/deg. Interestingly, cut-off spatial frequency was higher and Snellen acuity was slightly better for his *right* eye (20/20) than for the left (20/30). This is the closest approximation to a medium frequency notch that we have observed in over fifty control subjects. This control subject had no history of visual problems and subsequent neurological examination revealed no disorder.

Fig. 3A shows a contrast sensitivity curve for Patient 1. All patients showed 'medium frequency' differences of at least 2:1 between the left and right eyes. All patients except No. 7 had similar Snellen acuities in the left and right eyes, and in no case was acuity worse than 20/30.

Experiment 1. Discrimination between Filtered Versions of the Letter 'E'

In preliminary experiments we varied letter contrast in order to find the contrasts required to attain 80 per cent correct discrimination between spatially-filtered 'E's at different viewing distances. For none of our available letter stimuli, however, was the maximum attainable contrast sufficiently high to allow measurements at the longer viewing distances required in this study. Therefore, we tried a second method, namely, to keep letter contrast constant at the highest level attainable and vary letter intensity (light scatter from the surround into the central aperture, although small, was not zero so that some minor contrast changes were associated with changes of letter intensity). For Patient 2 this method of quantifying letter discrimination was adequately sensitive to show a dip in the discrimination plot for the left eye which was not evident in the data for the right eye and could not be explained by refractive errors. However, this method was not sensitive enough to clearly bring out variations in letter discrimination in other patients who showed smaller effects.

With the aim of achieving greater sensitivity to failures in letter discrimination we tried a third method. This third method of quantifying letter discrimination was to measure the percentage correct discrimination with the letters held at a fixed intensity and contrast. Fig. 3B showed that this third method clearly revealed failures in letter discrimination that occurred at a specific viewing distance. All four patients tested with the pair of spatially-filtered 'E's showed dips in letter discrimination at a particular viewing distance. We found that the percentage correct plot was indeed somewhat more sensitive than the intensity plot, providing that appropriate fixed levels of intensity and contrast were selected for the percentage correct plot (for instance, the percentage correct data were useless if the intensity or contrast was so low that all discriminations were at chance or if the intensity or contrast was so high that discrimination was always near 100 per cent correct).

Since we selected the intensity of the letter pair so as to best bring out the dip in the percentage correct plot, absolute values of percentage correct judgements cannot be compared between different figures (for example, figs. 3C and D). Only the presence and location of the dips should be compared. Note also that we plotted percentage correct discriminations on a linear rather than on a probability scale. This had no appreciable influence on the viewing distance for minimum discrimination and therefore the choice of scale did not affect our conclusions. However, it is not possible to make other than rather rough estimations of the spatial frequency bandwidth of the patients' contrast loss on the basis of our letter discrimination plots. For example, our technique probably exaggerates the narrowness of the loss in figs. 3B and C.

We found that discrimination between the spatially filtered 'E/E' pair could not be predicted from visual acuity measured by either the high-contrast grating or the Snellen test. On the other hand, 'E/E' letter discrimination could be accurately predicted from the shape of the contrast sensitivity curve. For example, the contrast sensitivity curve for Patient 1 showed a dip for the left eye that was most marked near a spatial frequency of about 7-12 cycles/deg and this dip was not present for the right eye. Correspondingly, the 'E/E' letter discrimination for Patient 1 showed a dip for the left eye that was not present for the right eye. Furthermore, this dip in letter discrimination reached its greatest depth at a viewing distance of 400 cm to 750 cm (mean 575 cm), and at this distance the spatial frequency band 2.0 to 2.5 cycles/width of the 2.22 cm-wide letter covered 9 to 11 cycles/deg of visual angle, a band of spatial frequencies that fell neatly into the 'medium frequency' notch in the patient's contrast sensitivity curve (fig. 3A). Further, 'E/E' discrimination for the two eyes became equal at a viewing distance of 730 cm and at this distance the range 2.0 to 2.5 cycles/width spanned 12 to 15 cycles/deg, a band of spatial frequencies just at the extreme upper limit of the 'notch' in fig. 3A. (The 'E's differed only over the range 2.0 to 2.5 cycles/letter width.)

Except for Subject 9, none of the nine control subjects showed dips in discrimination for the 'E/E' pair that could not be accounted for by differences in visual acuity at particular distances. For all control subjects, percentage correct discrimination for the 'E/E' test fell to chance level (i.e. 50 per cent) at a viewing distance of about 1000 cm. Since the difference between the two 'E's was entirely confined to the band of spatial frequencies between 2.0 and 2.5 cycles/letter width, and since the width of 'E' was 2.2 cm, we can say that the physical difference between the two 'E's was confined to the band of spatial frequencies between about 16 and 20 cycles/deg when discrimination between the 'E's fell to chance level. This band of spatial frequencies was located on the steeply descending portion of the contrast sensitivity curve where visual contrast sensitivity was low.

Experiment 2. Discrimination between the Spatially-filtered Letters 'O' and 'C'

Five out of the 6 patients tested with the filtered 'O/C' pair showed a failure in discrimination at a particular viewing distance. The sixth patient's data were too variable to allow a conclusion. In the 4 patients tested with both the filtered 'E/E' and the filtered 'O/C' pairs, the failure of discrimination occurred at roughly the same viewing distance for the two letter pairs. Fig. 3C illustrates our filtered 'O/C' data.

Apart from Control Subject 9, none of the 9 control subjects showed any significant failure in discrimination of the filtered 'O/C' pair that could not be attributed to acuity differences at particular viewing distances (that is, to refractive error). Control Subject 9 had a failure of 'O/C' discrimination over a range of viewing distances between 430 and 700 cm. Over this range of distances the spatial frequency range 1.5 to 2.5 cycles/width corresponded to 5 to 14 cycles/deg, and this fitted well with the 7 to 20 cycles/deg notch in his contrast sensitivity curve. (Ginsburg (1978, 1981) has shown that the spatial frequency range 1.5 to 2.5 cycles/letter width is sufficient for letter recognition. The bandwidths of our 'O' and 'C' extended up to 2.5 cycles/letter width.)

Experiment 3. Discrimination between Unfiltered Letters 'O' and 'C'

Patient 1 showed a difference between discrimination for the left and right eyes when the unfiltered 'O/C' pair was used as the stimulus. Fig. 3D shows that the maximum difference between the left and right eyes' discrimination occurred near

400 cm (approximately the same as for the unfiltered 'O/C' pair, fig. 3C), and that discrimination was not significantly different for left and right eyes both at closer (100 cm) and longer (700 cm) viewing distances. Patient 3 showed a difference between the eyes at a somewhat longer viewing distance for the unfiltered than for the filtered 'O/C' pair. None of the 9 control subjects (including No. 9) showed any significant dips for the unfiltered 'O/C' pair.

Regan *et al.* (1977) proposed that a medium-frequency notch in the contrast sensitivity curve might degrade a patient's ability to disregard magnification when recognizing an object by its shape. Experimental evidence suggesting that this might occur in some patients is provided by the data of fig. 3D. (Note that our evidence is restricted to the simple case of two-alternative *discrimination*. Whether the conclusion holds for multi-alternative shape discrimination or, as proposed, for shape recognition, remains to be established).

Experiment 4. Discrimination between Filtered and Unfiltered Versions of the Same Letter

The comment of Patient 1 during the experiments of figs. 3B–D was that, at a viewing distance of 430 to 560 cm, a test letter appeared to spread out as a blob that filled the entire viewing screen but when she moved back to a viewing distance of 700 to 800 cm the letter was localized to the centre of the viewing screen and could be recognized again. This comment applied both to filtered letters and to unfiltered (i.e. sharp) letters.

This patient's informal comment suggested that she might not be able to distinguish unfiltered letters from filtered letters at 430 to 560 cm viewing distance, whereas she could distinguish them at a slightly longer (or closer) distance. In order to test that supposition we carried out the following formal psychophysical experiment.

We measured discrimination between an unfiltered 'O' and an 'O' filtered from zero to 2.5 cycles/letter width. We plotted percentage correct discriminations *versus* the density of the filter placed in front of either projector No. 1 or projector No. 2. The viewing distance corresponded to the dip already identified in the letter discrimination curve (fig. 3C). In this experiment the following two visual cues for discrimination are to be considered: (*a*) the spatial difference of the light distribution in the filtered letters. This spatial difference was present in all trials; (*b*) the difference in total light flux between the two letter stimuli. This light flux difference was varied, and in some trials was near zero.

The results were as follows. Using the unaffected (right) eye, Patient 1 correctly discriminated unfiltered from filtered 'O's with a probability around 20 to 25 per cent above chance, whether the unfiltered letter was brighter or dimmer or the same intensity as the filtered letter. Therefore, Patient 1 was not using brightness or total light flux as the sole cue for discrimination when she used her unaffected eye. We assume that she was using a spatial cue. On the other hand, when using the affected (left) eye, Patient 1 could not distinguish between the unfiltered and filtered 'O's when the two letters were of equal intensity or when they were within ±0.1 or ±0.2 log unit of equality. When an intensity difference of about 0.4 log unit was introduced between the letters, although discrimination rose to better than 30 per cent above chance, Patient 1 consistently selected the brighter letter rather than the unfiltered letter, whichever was the brighter letter. Therefore, when using her affected eye, Patient 1 did not at any time base the discrimination between unfiltered and filtered letters on spatial cues.

DISCUSSION

Contrast Sensitivity Losses in Patients with Multiple Sclerosis

The five examples of contrast sensitivity curves with unilateral 'medium frequency' losses of sensitivity confirm our previous report of such defects in patients with multiple sclerosis whose Snellen acuity and cut-off spatial frequency are unaffected (Regan *et al.*, 1977).

As previously pointed out by Bodis-Wollner (1972), for the case of a patient with a tumour affecting the visual cortex, visual acuity (e.g., Snellen acuity) may give no indication that vision is abnormal at lower spatial frequencies, even when the abnormality is gross. Fig. 3A underlines our previous practical point that, in multiple sclerosis, the sinewave grating contrast sensitivity test can aid diagnosis by revealing visual abnormality that is detected neither by the Snellen test, nor by measuring cut-off spatial frequency (Regan *et al.*, 1977; Zimmern *et al.*, 1979).

Prediction of Letter Discrimination from the Grating Contrast Sensitivity Curve

It is not self-evident that visual contrast thresholds measured with sinewave grating targets provide an adequate basis for predicting a subject's ability to recognize complex shapes, or his ability to discriminate between two different shapes either in high-contrast conditions or even at near-threshold contrasts. Whether such predictions can be made on the basis of either a simple linear model or a physiologically-plausible nonlinear model is a question that can only be settled by experiment. Our plan here has been to adopt a cautious step-by-step approach to these questions. Leaving aside problems of superthreshold *versus* threshold perception, and shape recognition *versus* multi-alternative discrimination, we restricted ourselves to comparing sinewave grating contrast thresholds with two-alternative letter discrimination performance.

For Experiments 1 and 2 we synthesized spatial test stimuli, each of which approximated a simple sinewave grating as closely as we could arrange, while yet being a clearly recognizable letter. To this end we restricted each letter to a moderately narrow spatial frequency band. The letter pairs in Experiment 1 differed only over the range 2.0 to 2.5 cycles/width, and in Experiment 2 only over the range 1.5 to 2.5 cycles/width, so that Experiments 1 and 2 followed the rationale of figs. 1A–F.

Experiment 1 clearly showed that, in patients with multiple sclerosis, elevations of *contrast detection threshold* measured with narrow-bandwidth sinewave gratings predicted defects of letter *discrimination* between two moderate-bandwidth test stimuli that differed only in bandwidth. In Experiment 2 we tried to extend this finding closer to shape discrimination in everyday vision by measuring discrimination between different letters rather than between different bandwidth versions of the same letter. We found that the conclusions of Experiment 1 clearly hold also for the discrimination of moderate-bandwidth versions of different letters. (In Experiment 2 the differences between the letter pairs were limited to the relative amplitudes and phases of spatial frequencies in the 1.5 to 2.5 cycles/width band.) Letter discrimination curves were predictable from grating contrast thresholds for normal eyes as well as for abnormal eyes. The letter discrimination curves of normal eyes were smooth, and similar for left and right eyes, in accord with the grating contrast sensitivity curves.

Refractive error or presbyopia might provide a possible explanation for our finding that patients with a notch in their sinewave contrast sensitivity curve showed degraded letter discrimination at a particular viewing distance. We excluded this trivial explanation by showing that visual acuity did not vary over the range of viewing distances that encompassed the marked changes of letter discrimination.

Experiment 3 resembled Experiment 2, except that the pair of different letters was of considerably greater bandwidth. In fact, we used a pair of ordinary Snellen letters. Thus the rationale of Experiment 3 followed figs. 1G–I.

Unequivocal results were obtained from the one control subject who had a (marginal) medium-frequency notch in the contrast sensitivity curve. This subject had no appreciable difference in discrimination between left and right eyes for the unfiltered broadband letter pair, suggesting that at viewing distances for which low cycle/width information fell into the notch he was able to use the remaining high cycle/width information for letter discrimination, when it was available. Unequivocal, but contrary results were obtained from one patient who had a pronounced medium-frequency notch. At viewing distances for which low cycle/width information fell into the notch she was unable to use the available high cycle/width information for letter discrimination. This may be due to a combination of reasons. The patient's notch was considerably deeper and broader than the control subject's, and extended closer to the upper end of the contrast sensitivity curve so that with unfiltered letters the patient's situation may have approximated figs. 1D–F, whereas the control subject's situation approximated figs. 1G–I.

Insufficiency of Visual Acuity as a Measure of Form Vision

Some patients with multiple sclerosis have visual defects that do not show up as reduced visual acuity, whether visual acuity is tested with standard high-contrast Snellen letters or by measuring the cut-off spatial frequency. This is because the defects are restricted to intermediate or low spatial frequencies without appreciably affecting contrast sensitivity at high spatial frequencies. It is clear why cut-off frequency would not detect such a visual defect. On the other hand, ordinary Snellen letters include an appreciable range of spatial frequencies so that they test, not merely one high spatial frequency, but an appreciable region of the contrast sensitivity curve that, in principle, might be sufficiently wide to ensure that the standard Snellen test revealed contrast sensitivity losses at intermediate as well as at high spatial frequencies. Indeed, some empirical studies of normal vision have shown that Snellen acuity is not accurately predicted by cut-off frequency (Gstalder and Green, 1971; Bodis-Wollner and Diamond, 1976; Ginsburg 1981), but is related to the shape of the contrast sensitivity curve (Ginsburg, 1978, 1979, 1981).

Here we report that neither cut-off frequency nor Snellen acuity accurately predicted the variability of contrast sensitivity among 18 control eyes, confirming the finding in previous studies on 68 control eyes (Regan *et al.*, 1977) and on 22 control eyes (Regan *et al.*, 1980) that contrast sensitivity at spatial frequencies near 5 cycles/deg shows at least ±2:1 inter-subject variability even between control subjects who have 20/20 Snellen acuities and similar cut-off frequencies. This dissociation may be related to the reported differences in the detection and identification of complex objects among pilots and other military personnel who have similar cut-off frequencies and Snellen acuities (Ginsburg, 1979).

Our findings indicate that the standard high-contrast Snellen test might usefully be supplemented with a test of visual sensitivity to intermediate spatial frequencies (for example, low-contrast Snellen letters) in visual selection for the many occupations where excellent vision is essential for safety. Our findings also indicate that, by testing vision with low-contrast Snellen letters as well as with the standard high-contrast letters the neurologist or ophthalmologist might detect visual dysfunction in a considerably greater proportion of patients with multiple sclerosis than when only the standard high-contrast Snellen test is used.

SUMMARY

Several disorders that affect the visual pathway can degrade contrast sensitivity to low and medium spatial frequencies without affecting visual acuity. We previously suggested that a medium-frequency 'notch' in the sinewave grating contrast sensitivity curve might degrade a patient's ability to disregard magnification when recognizing an object's shape. In this way, a visual sensory defect might sometimes masquerade as a cognitive disorder (namely, object agnosia), and this might be misleading in a disease such as multiple sclerosis which is associated with both sensory and cognitive disturbances.

Here we report a first step towards exploring this suggestion. We have measured the accuracy with which multiple sclerosis patients could discriminate between pairs of letters, choosing patients who had a medium-frequency loss of contrast sensitivity in one eye, but not in the other eye, though both eyes had similar Snellen acuities and cut-off spatial frequencies. First we compared a patient's affected and unaffected eyes in their ability to discriminate (*a*) between pairs of spatially-filtered letters and

then (*b*) between pairs of ordinary Snellen letters. This checked whether a patient's ability to *discriminate* between different broad-bandwidth (letter) stimuli could be predicted from the contrast sensitivity curve, that is, his ability to *detect* narrow-bandwidth (sinewave grating) stimuli. (Note that our simple experiments did not test a patient's ability to *recognize* a particular shape in the sense of discriminating it from many alternative possibilities.)

Patients discriminated a letter pair about as well when using an eye whose contrast sensitivity curve had a marked spatial-frequency 'notch' as when using the good eye, provided that the letters were of either large or small angular size, but not when they were of intermediate angular size. This difficulty in discrimination could occur with ordinary Snellen letters as well as with spatially-filtered letters. Thus, some patients with a 'notch' experienced degraded ability to disregard magnification when discriminating the shapes of ordinary letters. Quite different results were obtained for normal eyes in both patients and control subjects: as one would expect, discrimination was progressively degraded as viewing distance was increased.

This difficulty of letter discrimination could not be predicted on the basis of visual acuity (whether measured as grating cut-off frequency or by using the Snellen test), but it could be predicted with fair accuracy from the 'notch' in the contrast sensitivity curve.

ACKNOWLEDGEMENTS

We thank patients and control subjects for their good-humoured co-operation. We thank Dr L. Harris for his comments on an earlier version of this paper. This research was supported by the MRC of Canada (Grants MS-6495 and ME-7002) and by the National Eye Institute (Grant 79-EY652). J.R. was supported by a Natural Sciences and Engineering Research Council of Canada scholarship.

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(*Received August 26, 1980*)

Brain (1981), **104**, 351-368

LARYNGEAL ABDUCTOR PARALYSIS IN MULTIPLE SYSTEM ATROPHY

A REPORT ON THREE NECROPSIED CASES, WITH OBSERVATIONS ON THE LARYNGEAL MUSCLES AND THE NUCLEI AMBIGUI

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INTRODUCTION

SOME patients with the Shy-Drager syndrome—progressive autonomic failure associated with multiple system atrophy—develop laryngeal stridor in the later stages of the disease. This feature of the syndrome has received little attention until the last few years. Stridor is not mentioned in the clinical reviews of Shy and Drager (1960) and of Thomas and Schirger (1970) or in the sections of the *Handbook of Clinical Neurology* dealing with the Shy-Drager syndrome by Roessmann (1975), Schwartz (1975) and Barr (1979). Early reports of this complication are those of Bannister, Ardill and Fentem (1967, Case 4) and of Martin, Travis and van den Noort (1968; Case 11). The patient in the latter case suffered from stridor, leading to cyanosis and requiring tracheostomy. Examination of the larynx showed bilateral abductor paralysis of the vocal cords. A post-mortem was performed, but did not reveal the cause of the paralysis. More recently Israel and Marino (1977) described a similar case, successfully treated by tracheostomy; and Guilleminault, Tilkian, Lehrman, Forno and Dement (1977) reported a case of the Shy-Drager syndrome, shown post mortem to be due to multiple system atrophy, with unilateral vocal cord paresis, in which death was thought to have been due to apnœa during sleep.

It now appears, from the work of Williams, Hanson and Calne (1979) that abductor paralysis, of a degree which endangers life, is fairly common in this disease. It was present in 8 out of 12 unselected Shy-Drager patients reported by Williams *et al.* (1979), presenting as excessive snoring and stridor, and sometimes as sleep apnœa, and was regularly relieved by tracheostomy. But whereas a certain amount is now known about the histological and chemical pathology related to autonomic failure, next to nothing is known of the pathological basis of selective laryngeal abductor paralysis. It is for this reason that we are presenting the clinical and pathological findings in three cases of the Shy-Drager syndrome with laryngeal palsy, treated in each instance by tracheostomy.

CASE REPORTS (*See* Table 1)

Case 1

J.L., male, aged 51 years at death. The main clinical features have already been published (Spokes, Bannister and Oppenheimer, 1979; Case 3). Briefly, the patient had suffered from a progressive illness, lasting four years, starting with orthostatic hypotension and impotence, and later developing urinary incontinence and parkinsonism. Studies on autonomic function showed a moderately severe sympathetic efferent defect affecting the heart, resistance and capacity vessels, impaired cholinergic control of sweat glands, and a cardiac vagal defect. The clinical diagnosis was Shy-Drager syndrome, that is, multiple system atrophy with autonomic failure.

During the last six months of his life he suffered from breathlessness on gentle exertion, and intermittent involuntary gasping during quiet breathing. During sleep there was a marked inspiratory stridor which was so noisy that it disturbed the other patients in the ward. At intervals the stridor ceased, and there was a period of apnœa lasting one to two minutes before the breathing (and stridor) started again. When he was awake, there was no stridor even after moderate exercise.

On indirect laryngoscopy by one of us (W.G.) both vocal cords were approximately twice the normal thickness. Nevertheless the most striking feature was the immobility of both vocal cords; the right was virtually fixed, while only a small amount of movement was present in the left. The glottic aperture at full abduction only measured 4 mm, while glottic closure was complete. An attempt to improve the aperture by a Woodman's operation (suturing the arytenoid cartilage to the thyroid to swing the vocal cord laterally) did not improve the airway sufficiently, so the patient was given a tracheostomy and speaking tube. He managed the tracheostomy well until his sudden death at home during his sleep. Death was attributed to a cardiorespiratory arrest.

Pathological Findings

The cause of death appeared to be respiratory failure. There were no significant changes in viscera examined post-mortem.

(1) *CNS.* The brain weighed 1320 g and was normal externally. The right half was used for histological examination, the left half being reserved for biochemical studies. On slicing, the only naked-eye changes were shrinkage and discolouration of the right putamen and loss of pigment in the substantia nigra.

Microscopic changes were those of mutiple system atrophy, of striatonigral type, with cell loss and gliosis in the lateral and posterior parts of the putamen, in the lateral and caudal parts of the substantia nigra, and to a lesser degree in the locus cœruleus. Other structures commonly involved in multiple system atrophy—pontine nuclei, inferior olives, cerebellar Purkinje cells, and vestibular and dorsal vagal nuclei—were not obviously affected. No Lewy inclusion bodies were found.

In view of the patient's laryngeal palsy, the right nucleus ambiguus was examined in serial sections. The findings are described below.

TABLE 1. CLINICAL FEATURES

Case No.	*Age at death*	*Sex*	*Duration of autonomic symptoms (yrs)*	*Parkinsonism*	*Cerebellar signs*	*Bulbar signs*	*Pyramidal signs*	*Nocturnal apnœic attacks*	*Nocturnal stridor (yrs)*	*Bilateral abductor paralysis*	*Tracheostomy required*
1	51	M	4	+	○	+	+	+	1	+	+
2	70	F	3	+	○	+	+(R)	+	1	+	+
3	60	M	6	○	○	+	○	+	5	+	+

+ = present. ○ = absent.

TABLE 2. MEAN CELL COUNTS, WITH SEM, ON LATERAL HORNS OF THORACIC CORD

	Controls	*Case 1*	*Case 2*	*Case 3*
Upper third	15.8±1.0 (48)	8.1±0.5 (48)	6.8±0.7 (40)	4.9±0.4 (40)
Middle third	9.2±0.7 (48)	2.8±0.3 (48)	2.9±0.3 (40)	2.7±0.4 (20)
Lower third	9.5±0.7 (48)	3.5±0.4 (40)	3.5±0.3 (40)	3.2±0.2 (40)

Figures in brackets show number of counts at each level. For method, *see* Oppenheimer (1980).

Cell counts were carried out on multiple sections of thoracic cord (for method, *see* Oppenheimer, 1980). These showed reduction of intermediolateral column cells to about two-fifths of normal values (*see* Table 2). Anterior horn cells and long tracts appeared normal.

No abnormalities were found in sensory and sympathetic ganglia, cœliac plexus, nerves, muscles, pharynx, intestine, bladder, skin or viscera.

(2) *Larynx—gross appearances*. The epiglottis, laryngeal cavity and upper trachea were congested. The right posterior crico-arytenoid muscle appeared extremely thin, but with normally orientated fibres. On the left side the fascia was thickened as the result of the Woodman's operation and no definite muscle fibres were identified. The other intrinsic muscles were of normal size. The recurrent laryngeal nerves were not examined.

Microscopic appearances. The right posterior crico-arytenoid muscle was seen as a thin strip covering the posterior surface of the cricoid cartilage. Most of the muscle fibres showed marked reduction in size. In addition there was a grouping of sarcolemmal nuclei and some lipofuscin deposition. The left posterior crico-arytenoid muscle showed similar changes, but there was also an extensive fibrosis as noted grossly. These appearances suggested a myopathy, without convincing evidence of denervation. The left crico-thyroid muscle showed fibrosis, but the right crico-thyroid muscle appeared normal. The inter-arytenoid, lateral crico-arytenoid and thyro-arytenoid muscles appeared normal.

Summary of Pathological Findings

Multiple system atrophy, with lesions in putamen, substantia nigra and intermediolateral columns; atrophy of posterior crico-arytenoid muscles.

Case 2

M.B., female, aged 70 years at death. The laryngological aspects of this case have already been reported (Thomas, 1978). The patient was achondroplastic, with an achondroplastic son. She was first seen by a neurologist (Professor W. B. Matthews) at the age of 68 years, having suffered from stridor, especially at night, for the past few months. She was taken to hospital in Oxford after being found barely conscious at her home. On examination, apart from the usual features of achondroplasia, there was ataxia affecting the trunk, moderate cogwheel rigidity in the limbs, brisk tendon reflexes with left extensor plantar response, and urinary incontinence. There was severe postural hypotension, the blood pressure being 105/75 lying, falling to 70/? on sitting. The patient could not stand long enough for the standing blood pressure to be measured. There was persistent stridor, mainly inspiratory during sleep, followed by periods of apnœa. A note made on direct laryngoscopy (Mr A. P. Freeland) showed that though both vocal cords moved there was bilateral abductor weakness, whereas in the report of indirect laryngoscopy (Thomas, 1978) a predominant right cord paresis was described. Treatment of the postural hypotension with fludrocortisone was not very effective. Anti-parkinsonian drugs were not given. The patient died in congestive heart failure following an episode of respiratory arrest. The clinical diagnosis (Professor W. B. Matthews) was of Shy-Drager syndrome, with achondroplasia.

Pathological Findings

The body was that of an elderly, achondroplastic woman. General necropsy findings included pulmonary œdema, benign nephrosclerosis and an old hysterectomy.

(1) *CNS*. The brain weighed 1520 g and was externally unremarkable. On slicing, the only visible changes were a slight shrinkage in the posterior parts of the putamina and loss of pigment in the caudal parts of the substantia nigra.

Microscopic changes were those of multiple system atrophy, affecting the lateral parts of the putamina, the lateral and middle thirds of the substantia nigra, inferior olives, medial and lateral vestibular nuclei, dorsal vagal nuclei, and a narrow strip on the ventral aspect of the pons. Remaining basal ganglia, thalamus, hypothalamus, cerebral cortex and locus cœruleus appeared intact. No Lewy inclusion bodies were found.

The medulla oblongata was sectioned serially for examination of the nuclei amibigui. The findings are described below.

No tract degeneration was seen in the brain-stem and spinal cord. Anterior horn cells appeared normal. Counts on lateral horn cells (*see* Table 2) showed about two-fifths the normal number of intermediolateral column cells.

No abnormalities were found in sensory and sympathetic ganglia, nerves or skeletal muscles, other than those of the larynx.

(2) *Larynx—gross appearances*. Both posterior crico-arytenoid muscles were very atrophic, being represented by thin sheets of muscle fibres about 1 mm in maximum antero-posterior thickness on the left side and 1.5 mm on the right side (figs. 1 and 2). The other intrinsic laryngeal muscles appeared normal. The recurrent laryngeal nerve, and its branch to the posterior crico-arytenoid muscles on each side, were demonstrated and appeared normal.

Microscopic appearance. Histological examination confirmed the gross atrophy of both the posterior crico-arytenoid muscles. There were large numbers of very small muscle fibres and a few small groups of fibres of normal size. In addition there was lipofuscin deposition in the sarcoplasm of some muscle fibres, chains of sarcolemmal nuclei and areas of sarcoplasmic necrosis surrounded by histiocytic

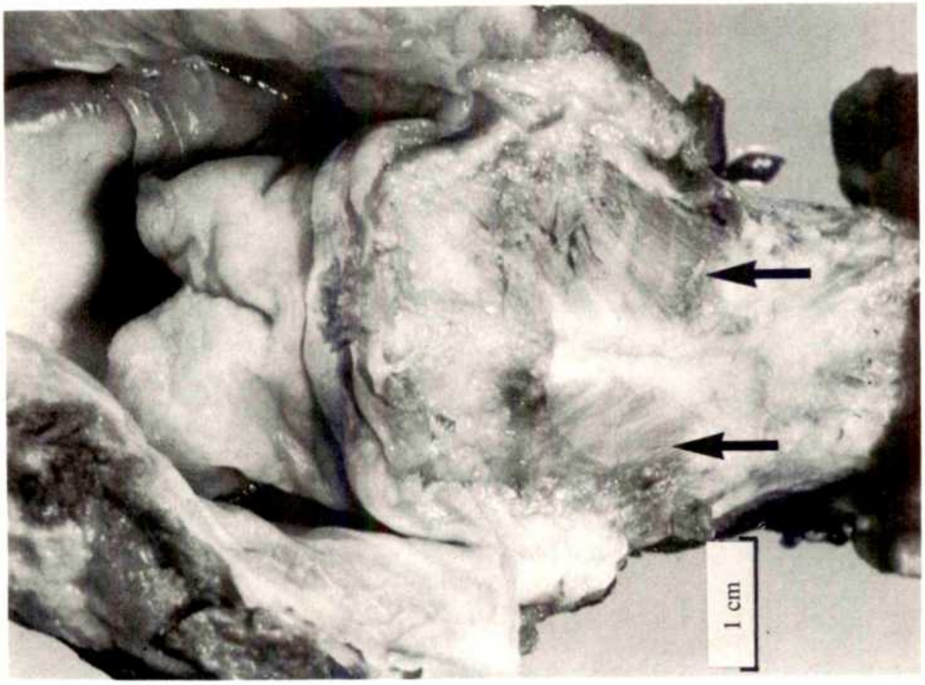

FIG. 1. View of larynx from behind in Case 2. The posterior crico-arytenoid muscles (arrows) are markedly thinned.

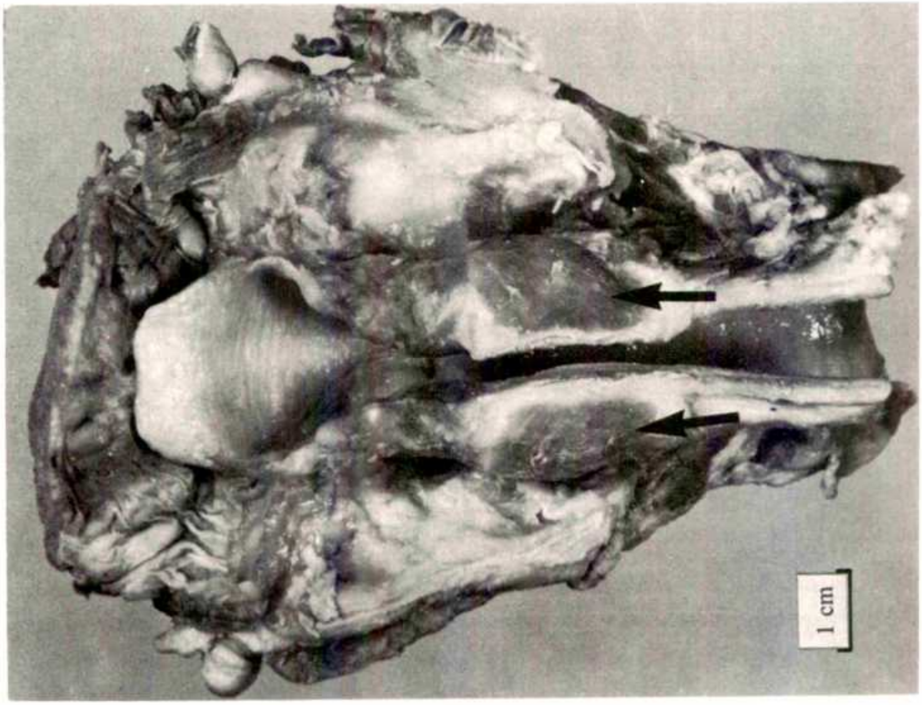

FIG. 2. View of normal larynx from behind for comparison with fig. 1. The posterior crico-arytenoid muscles (arrows) are fleshy and protuberant.

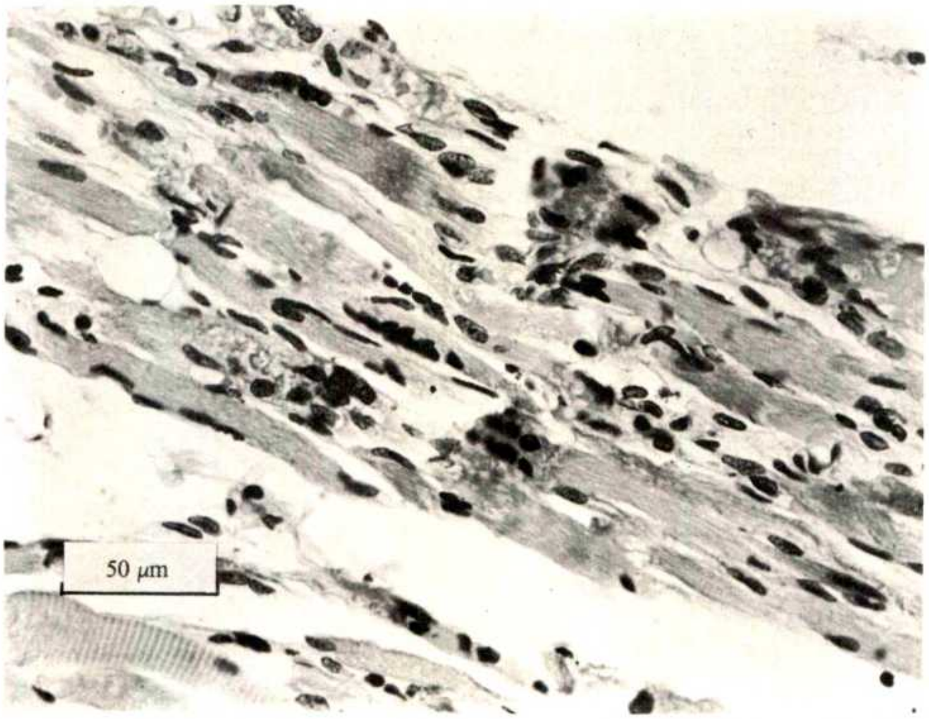

FIG. 3. Posterior crico-arytenoid muscle from Case 2. Some fibres are atrophic. There is clumping of nuclei in rows and necrosis of sarcoplasm with histiocytic reaction and pigment deposition. (Hæmatoxylin and Eosin).

cells (fig. 3). The lateral crico-arytenoid, the thyro-arytenoid, the inter-arytenoid and the crico-thyroid muscles on both sides showed moderate degrees of myopathic change similar to that seen in the posterior crico-arytenoid muscles, except that there was no atrophy.

The recurrent laryngeal nerves showed no gross abnormality, but fibre counts were not done.

Summary of Findings

Achondroplasia, and multiple system atrophy affecting putamen, substantia nigra, pons, olives, vestibular and dorsal vagal nuclei, and intermediolateral columns. Atrophy of posterior crico-arytenoid muscles.

Case 3

D.C., male, aged 60 years at death. The illness began seven years before death with fainting episodes. Postural hypotension was discovered. After trial of various pressor drugs, the fainting attacks were stopped by head-up tilting of the patient's bed and oral fludrocortisone. Two years later he developed urinary hesitancy, incontinence and impotence. There was failure to sweat on body heating. There were no other important neurological deficits, but both plantar responses were extensor. Studies of autonomic function indicated moderately severe sympathetic efferent lesions affecting the heart and resistance and capacity vessels. There was impaired cholinergic control of sweating, and a cardiac vagal defect. The clinical diagnosis was of Shy-Drager syndrome.

When the patient was first seen by one of us (W.G.), there was no breathing difficulty or stridor on examination, even after moderate exercise, but he gave a history of stridor developing at night, initially inspiratory but later also expiratory. The stridor had been witnessed by his family, who found it alarming, and there had been two incidents at night when he had been found cyanosed following a period of respiratory arrest. On indirect laryngoscopy the vocal cords were thickened, and there was some marginal œdema, particularly of the left vocal cord. The vocal cord movements were filmed and analysed by a group of ENT surgeons at a clinical meeting. The consensus of their opinions was that abduction of the cords was reduced in amplitude and speed and was incomplete, but adduction was completely normal. Direct laryngoscopy was performed under general anæsthesia. The supraglottic tissues were loose, and fell in folds down into the larynx. It was decided to take a biopsy from the free edge of the cords, but before this was accomplished the patient had a transient cardiac arrest and the procedure had to be halted. Following this episode he had a period of profound hypotention which lasted nearly two days.

During the next few months the stridor at night increased and became very worrying. The stridor was recorded, and consisted of a coarse inspiratory and expiratory sound like a donkey braying. It was decided that tracheostomy was required, and this was performed without complication with a very light general anæsthetic and extensive local anæsthetic infiltration. During the next six months the tracheostomy functioned well. He was then admitted for shortening of the tracheostomy tube, but during the night he had a cardiorespiratory arrest, from which he died after three days of artificial ventilation.

Pathological Findings

The body was that of a heavily-built middle-aged man, with a tracheostomy. The airways were clear, and there was no sign of infection in the lungs. Findings included chronic cystitis, chronic pyelonephritis (not severe) and a large nodular goitre.

(1) *CNS.* The left side of the brain was examined histologically, the right side being reserved for chemical studies. Weight of brain 1430 g. Externally there was bilateral uncal grooving, and a gross herniation of the cerebellar tonsils, which were disrupted and hæmorrhagic. There were no naked-eye abnormalities on slicing.

Microscopically, severe acute hypoxic cell changes were present in nearly all parts of the brain. Long-term changes were seen in the substantia nigra, which showed moderate loss of neurons, with scattered deposits of extracellular melanin; in the inferior olive and medial vestibular nucleus, which showed moderate cell loss and gliosis; and in the cerebellar cortex, where there was patchy but locally severe loss of Purkinje cells.

No long-term changes were seen in the putamen or other basal nuclei, or in the locus cœruleus, pontine nuclei, or dorsal vagal nucleus. No Lewy inclusion bodies were seen. The upper part of the nucleus ambiguus was recognizable, but assessment of cell numbers was rendered impracticable by the widespread hypoxic cell changes.

No changes were seen in the long tracts of the brain-stem and cord. Anterior horn cells and thoracic nuclei appeared intact. Customary cell counts on ten levels of the thoracic cord showed reduction of cells in the lateral horns, to about one-third of normal numbers (*see* Table 2).

In the peripheral nervous system, embedded and frozen sections of Gasserian, spinal sensory and sympathetic ganglia, cœliac plexus, vagus, nerves of upper and lower limbs, and cranial and spinal striated muscles all appeared normal, excepting the larynx.

(2) *Larynx*. The ary-epiglottic folds were very œdematous. The false cords were markedly swollen and the lumen of the larynx was narrowed at this point. Cut surface showed hypertrophy of the seromucinous glands. There was a tracheostomy opening. Both posterior crico-arytenoid muscles appeared atrophic, and were reduced to about 0.15 cm maximum thickness (fig. 4).

The other intrinsic laryngeal muscles appeared normal. The recurrent laryngeal nerve and its branch to the posterior crico-arytenoid on each side appeared normal.

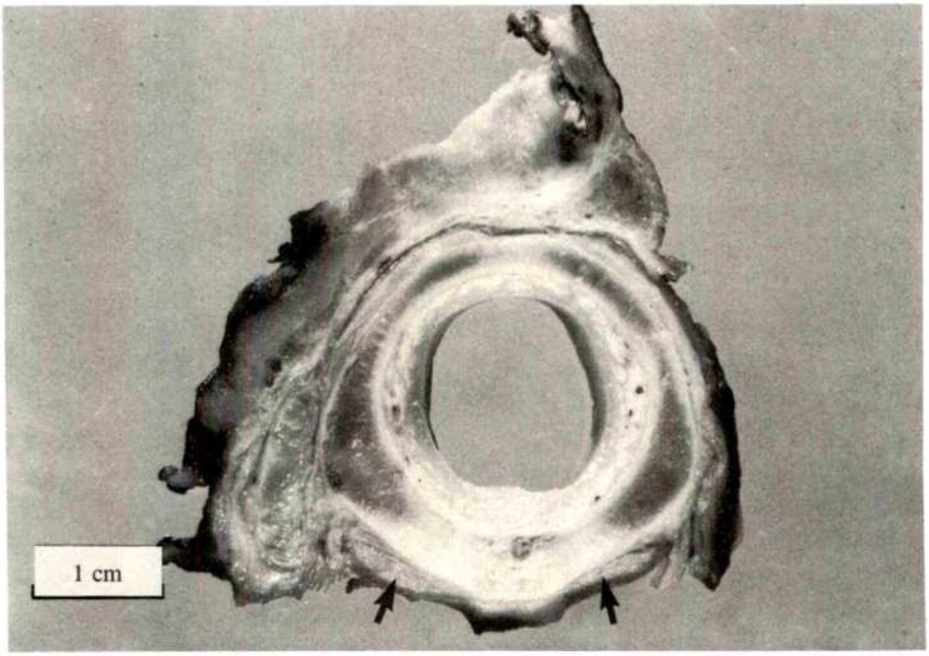

FIG. 4. Larynx from Case 3 sliced transversely in the region of the cricoid cartilage. The posterior crico-arytenoid muscles (arrows) are atrophic.

Larynx—microscopic appearances. Both posterior crico-arytenoid muscles showed areas of minute fibres and areas of normally sized fibres (figs. 5 and 6). The nuclei and sarcoplasm of the muscle, apart from changes in fibre size, appeared normal. These changes were typical of denervated muscle.

The inter-arytenoid muscle showed rows of sarcolemmal nuclei and lipofuscin deposition; the crico-thyroid, lateral crico-arytenoid and thyro-arytenoid muscles appeared normal.

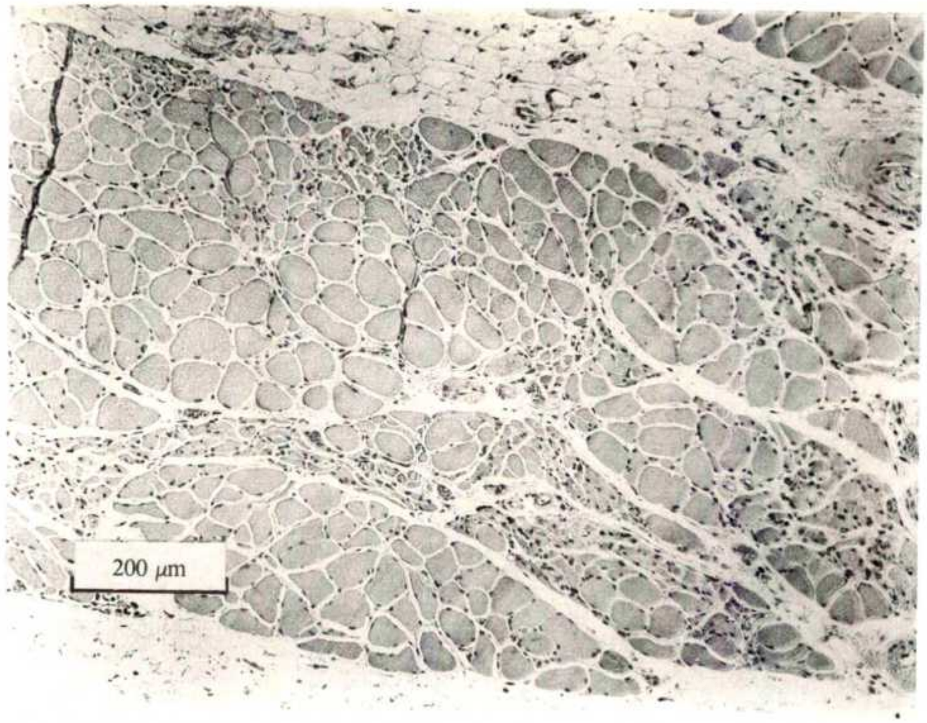

FIG. 5. Posterior crico-arytenoid muscle from Case 3. There are groups of atrophic muscle fibres, in contrast with the normal-sized fibres that fill most of the field. (Elastic van Gieson).

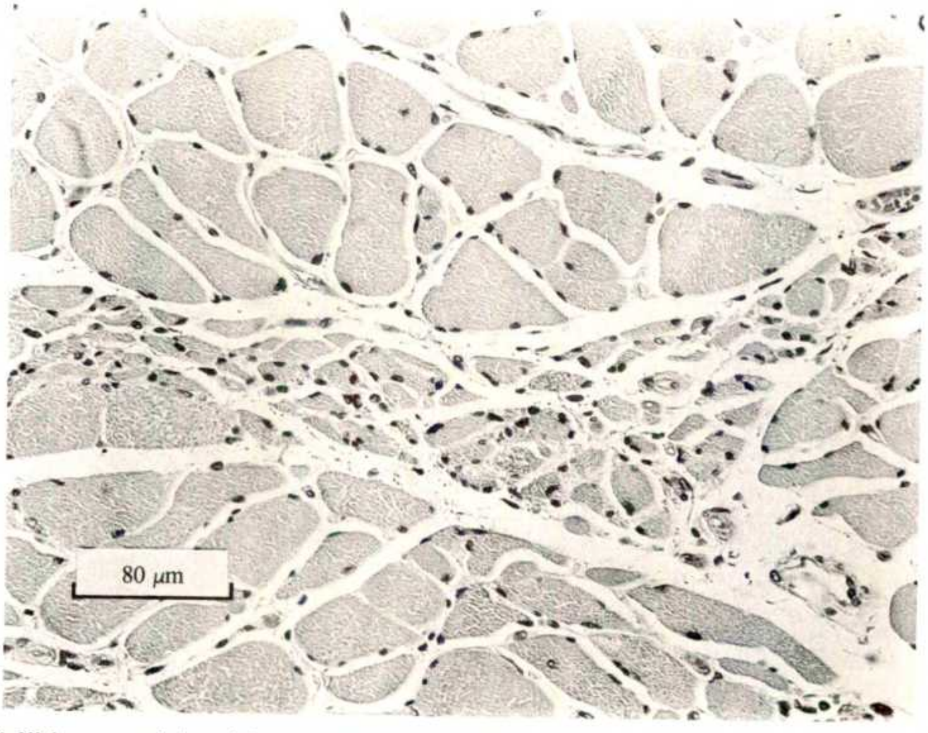

FIG. 6. Higher powered view of the posterior crico-arytenoid muscle in Case 3 to show a group of atrophic fibres surrounded by normal fibres. (Elastic van Gieson).

The recurrent laryngeal nerve, examined in transverse section at a point just inferior to the origin of the branch to the posterior crico-arytenoid muscle on each side, showed no focal abnormality. However, when compared with transverse sections of recurrent laryngeal nerves taken at the same situation in three normal post-mortem larynges there was a reduction of nerve fibre numbers, and the over-all diameters of the fibres appeared increased in both recurrent laryngeal nerves of Case 3 (figs. 7 and 8).

Summary of Findings

Multiple system atrophy, affecting substantia nigra, inferior olives, Purkinje cells, medial vestibular nuclei and intermediolateral columns. Terminal cerebral hypoxia causing swelling and herniation. Atrophy of posterior crico-arytenoid muscles, with loss of axons in recurrent laryngeal nerves.

Examination of the Nucleus Ambiguus (Cases 1 and 2)

The finding of muscular atrophy in a specific pair of laryngeal muscles in these three cases prompted a detailed examination of the nucleus ambiguus, which is generally believed to innervate the muscles of the larynx. For the present purpose, the nucleus ambiguus was defined as a column of typical somatic motor cells lying in the reticular formation of the medulla oblongata, between the dorsal accessory olive and the nucleus of the spinal tract of the trigeminal nerve, and extending from the lower end of the main olivary nucleus upwards to a point immediately below the facial nucleus.

Cell counts were carried out on Cases 1 and 2 and compared with controls. In Case 3, agonal hypoxic cell changes had made it impossible to distinguish motor cells from the rest. Two controls were used; the first from a woman of 70 years with Alzheimer's disease, and the second from a man of 62 years dying of renal failure. In neither case was there clinical evidence of brain-stem malfunction.

For the controls, and for Case 2, the procedure was the same. The whole of the medulla was embedded in paraffin, and serial transverse sections cut at 20 μm thickness. The sections were mounted 4 on a slide, and every fifth slide was stained with cresyl violet, giving a 1 in 5 sampling frequency. Counts were carried out on the nucleoli of cells, recognizable as motor cells by their size, shape and coarse Nissl bodies, lying in the position indicated by Olszewski and Baxter (1954) for the nucleus ambiguus. Slides including any part of the facial nucleus were not used for counting.

In counting there was rarely any doubt as to whether a particular cell had the characteristics of a motor neuron; but there were some difficulties, especially in the upper segments, in deciding whether a cell, or a cluster of cells, belonged to the nucleus ambiguus or to (for instance) the retrofacial nucleus. The impression was gained that the nucleus ambiguus is less compact and well defined than Olszewski and Baxter indicate. There are places where this nucleus appears to split into two or

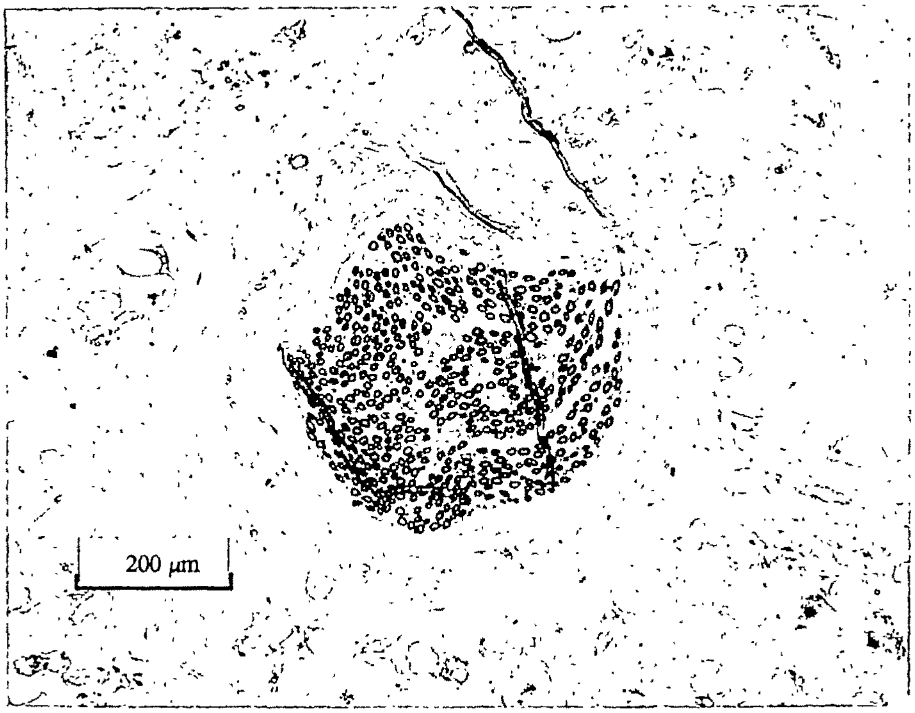

FIG. 7. Right recurrent laryngeal nerve in Case 3 just inferior to branch to posterior crico-arytenoid muscle. There is no focal abnormality, but the fibres appear larger and less numerous than in normal control. (Transverse section, 1 micron thick, embedded in methacrylate, Sudan black stain).

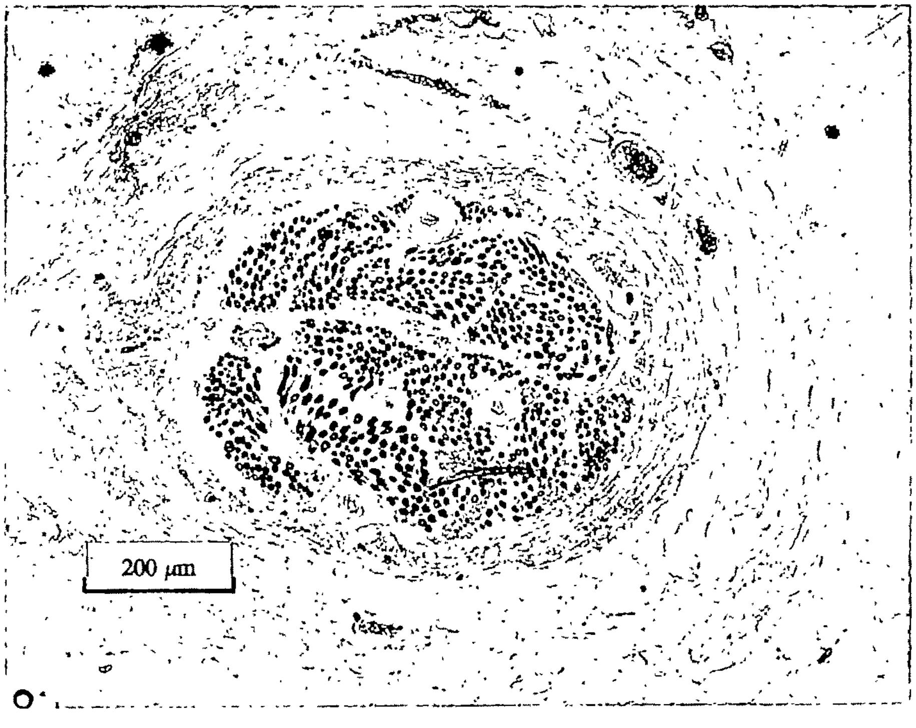

FIG. 8. Right recurrent laryngeal nerve from normal larynx taken from just inferior to branch to posterior crico-arytenoid muscle. There are more small fibres and a larger total number of fibres than in Case 3. (Transverse section, 1 micron thick, embedded in methacrylate, Sudan black stain).

three cell columns, of which the most ventral seems to run without interruption into the retrofacial nucleus; and isolated motor cells, morphologically indistinguishable from these, may be seen in the nearby lateral and medial reticular nuclei (nuclei medullæ oblongatæ lateralis et centralis of Olszewski and Baxter). In practice, cells were counted only if they lay within a circle 1 mm in diameter in the advertized position of the nucleus ambiguus.

In Case 1, only the right half of the medulla was available, the left side having been used for biochemical studies. The specimen was embedded in three transverse blocks and early sections from these were subjected to a variety of stains. The remainder was cut at 20 μm thickness, and the sections mounted 5 on a slide. Alternate slides were used for cell counting. Allowing for the gaps between the blocks, and for the fact that only one side was examined, the sampling frequency for the whole medulla lay between 1 in 4 and 1 in 5—a figure comparable with the controls and with Case 2.

Owing, partly no doubt, to anatomical variation and partly to differences in post-mortem handling, the lengths of the portions examined were different. The lengths were, approximately, 12.0 mm in Control 1; 13.2 mm in Control 2; 9.6 mm in Case 1; and 12.0 mm in Case 2. In each case the total length was arbitrarily divided into 6 equal segments, which were labelled A, B, C, D, E, F from above down. Table 3 shows the mean counts in each segment for each of the four cases. The comparison of the counts would be somewhat more accurate if corrections were made for the relative lengthening and shortening of the medulla in the four specimens; but such a correction would not materially affect the over-all impression, which is that there is no significant difference between the cases of laryngeal palsy and the controls.

TABLE 3. MEAN CELL COUNTS ON SINGLE NUCLEI AMBIGUI AT SIX LEVELS WITH SEM

Level	*Control 1*	*Control 2*	*Case 1*	*Case 2*
A	3.3±0.4 (40)	2.0±0.3 (40)	2.6±0.3 (40)	2.4±0.4 (28)
B	7.9±0.7 (40)	6.2±0.3 (48)	3.75±0.4 (40)	9.3±0.5 (40)
C	3.9±0.4 (40)	5.6±0.5 (40)	8.9±0.5 (35)	3.2±0.3 (40)
D	2.75±0.3 (40)	2.5±0.25 (48)	3.1±0.4 (40)	1.2±0.2 (40)
E	1.88±0.3 (40)	1.45±0.2 (40)	1.0±0.17 (35)	0.55±0.16 (40)
F	0.85±0.2 (40)	1.3±0.16 (48)	1.75±0.25 (40)	0.58±0.12 (48)

Figures in brackets show number of counts. Top level is A.

DISCUSSION

The laryngeal abnormality noted by one of us (W.G.) in Cases 1 and 3 was an incomplete abduction of both vocal cords, so that the glottic space was reduced, and the same was reported on direct laryngoscopy in Case 2. The adduction of the cords was not obviously affected. The findings might be thought to provide an unexpected confirmation of the validity of Semon's law, that the abductors are more susceptible than the adductors in a variety of lesions. In addition to the abductor weakness, the vocal cords were thickened to about twice the normal size, and the supraglottic tissues were lax, with some submucosal œdema.

The mainly inspiratory stridor which developed at night may have been partly due to the supraglottic tissues being drawn down into the larynx during inspiration and plugging the airway. The collapse of these tissues during sleep is due to loss of muscle tone (Gastaut, Tassini and Devan, 1966). However, the unusually musical character of the stridor was not like the noise produced by the collapse of the tongue and associated structures in a subject prone to snoring. The character of the inspiratory stridor in these patients was more suggestive of an obstruction at a laryngeal level. It is suggested that during sleep the abductor weakness became more pronounced, leading to narrowing of the glottis. There are several laryngeal muscles responsible for adducting the vocal cords but only the posterior crico-arytenoid muscle abducts the cords, so that this small muscle has a vital role in maintaining the airway. If the laryngeal abductors fail selectively in the Shy-Drager syndrome, then this failure is accentuated during sleep. A possible explanation concerns the mechanisms providing tone to the laryngeal muscles. During unconscious breathing, the laryngeal tone is delicately adjusted to favour the laryngeal abductors so that the laryngeal inlet remains patent. Moreover, the vocal cords are adjusted so that they remain sufficiently taut to prevent them flapping noisily to and fro during the course of respiration. It seems likely that tonic influences arise in the reticular system and pass to the nucleus ambiguus to allow interaction with the motor control of the larynx. This mechanism may be selectively damaged in multiple system atrophy, with the result that the laryngeal inlet narrows and the cords become flaccid. The flaccid cords may cause the peculiar predominantly inspiratory noise which characterizes these patients. The combination of lax supraglottic tissue plugging the glottis and defective vocal cord abduction could also have led to secondary alveolar hypoventilation, which caused periodic nocturnal apnœa with disturbed sleep and daytime somnolence, and to secondary cardiovascular and respiratory problems (Thomas, 1978).

In each of these three patients there was a striking degree of atrophy affecting both posterior crico-arytenoid muscles, but not the other intrinsic laryngeal muscles. The microscopic appearances in the posterior crico-arytenoid muscles in these cases indicate two forms of pathological change which are not necessarily related to each other. One form of change, which was conspicuous in Case 3 and probably present in Case 2, was the marked atrophy of groups of muscle fibres. These appearances suggest a denervation type of atrophy. The other change, which was pronounced in Case 1 and to minor degree in Case 2, was in the nature of a myopathic affection. Much less pronounced but variable degrees of the same changes may be found in all normal posterior crico-arytenoid muscles from the age of 13 years onwards (Guindi, Michaels, Bannister and Gibson, 1981) so that, although confusing when appearing together with the changes of denervation in Cases 2 and 3, they may be discounted in relation to the multiple system atrophy and autonomic failure in these patients. Similar myopathic changes were seen in other intrinsic laryngeal muscles in Cases 2 and 3; these changes are normally found only in the posterior crico-arytenoid muscles in normal adult larynges. We have recently observed such changes, however, in larynges bearing carcinomas, both with and without previous irradiation. It seems possible that they represent a non-specific reaction of the intrinsic laryngeal muscles to local muscular derangement.

The selective bilateral paralysis of posterior crico-arytenoid muscles in our three patients calls for an explanation. A similar problem is discussed in a recent article by Cruse, Edwards, Smith and Wyllie, (1979) concerning myopathic changes, leading to fibrosis, in the crico-pharyngeus muscle. Theoretically, several possibilities must be considered. First, the lesion might be simply an exaggeration of the myopathic changes (themselves still unexplained) observed by Guindi *et al.* (1981) in normal subjects. In our Case 1, the histological appearance of the posterior crico-arytenoid muscles could be regarded as 'myopathic'; in Case 2, however, and still more in Case 3, the appearances are strongly suggestive of denervation. Secondly, it might be suspected that the selective lesion of the posterior crico-arytenoid in normal subjects is a result of the proximity of the œsophagus to this muscle, which may be subjected to trauma during the passage of hard boluses or hot drinks. If this were so, the same traumatic agents might damage the nerve bundles supplying the muscle, with resulting denervation. In that case there might be evidence of axonal damage in the form of chromatolysis in the relevant part of the nucleus ambiguus, which supplies the motor fibres of the laryngeal muscles. Thirdly, there might be a primary neuronal degeneration in the nucleus ambiguus, as an extra item in the list of structures involved in the patients' multiple system atrophy. With this possibility in mind, we attempted to examine the nucleus ambiguus in our patients, and to compare them with normal controls. In our Case 3, this was found to be impracticable because of ischæmic cell changes in the brain-stem. In Cases 1 and 2, we were unable to find clear-cut differences from the control material. Counting of motor cells in the nucleus ambiguus at various levels (*see* Table 3) gave comparable figures for patients and controls, and there were no other signs of cell loss, such as neuronophagia or focal glial proliferation. We were hampered in this pursuit by not knowing precisely which part of the nucleus serves to innervate the posterior crico-arytenoid muscle. The standard work on this topic is that of Szentágothai (1943), who made stereotactic lesions in the nucleus ambiguus of cats, and looked for degenerating motor endings in individual laryngeal muscles. He reported that the most rostral part of the nucleus supplies the crico-thyroid muscle, the part immediately below this supplying the posterior crico-arytenoid, the rest of the laryngeal muscles being innervated by the more caudal parts. The corresponding data for the human larynx have not, as far as we know, been published.

We have had some difficulty in interpreting a recent report by Lapresle and Annabi (1979), describing a woman with olivo-ponto-cerebellar atrophy who developed a velo-pharyno-laryngeal paralysis seven years before her death at the age of 75 years. The report says 'The medulla was studied serially and all the sections stained. The nuclei ambigui were visible in 174 sections. The number and appearance of the neurons were normal in the upper third of both nuclei ambigui. In contrast, there was severe involvement of the lower two-thirds (110 sections) of these structures; neurons had almost completely disappeared and the few remaining cells were atrophic and hyperchromatic; a mild gliosis was noted.' The authors conclude from this that the innervation of the velopharyngolaryngeal musculature is from the lower two-thirds of the nucleus ambiguus. Unfortunately, they do not appear to have examined the actual muscles. There are several reasons for hesitation in accepting this report. In the first place, the human ambiguus is about 1½ cm long. A complete set of sections, cut at 20 μm, would therefore comprise about 750 sections, as against the authors' figure of 174. The authors do not state their limits for the upper, middle and lower thirds of the nucleus ambiguus; and they do not indicate whether they examined control material. There is normally a fairly sharp change in the cell population of this nucleus at the level of the upper end of the hypoglossal nucleus, with about 15 cells per nucleus per 20 μm section above, and from 1 to 5 cells below this. Our observations confirm with Olszewski and Baxter's (1954) description. We are not fully convinced that Lapresle and Annabi are describing a pathological change in the nucleus ambiguus.

The lack of histological changes in the nucleus ambiguus in Cases 1 and 2 does not of course imply normal function during life. Recently (Spokes *et al.*, 1979), it has been shown that in cases of multiple system atrophy biochemical defects may be the basis of loss of function in central structures, where no neuronal loss can be detected by existing histological methods. A biochemical defect therefore seems a possible explanation for the denervation of laryngeal muscles in these cases. We also have evidence, in Case 3, of a loss of fibres in the recurrent laryngeal nerves.

The association of laryngeal abductor palsy with the Shy-Drager syndrome (multiple system atrophy with autonomic failure) is now well documented (*see* Williams, *et al.*, 1979). Laryngeal palsy in cases of multiple system atrophy without autonomic failure is a less familiar association, but the case described by Lapresle and Annabi (1979) may be taken as an example. We are led to suppose that the nucleus ambiguus (or at least that part of it which supplies the abductor muscles) is one of the structures at risk in multiple system atrophy, along with the striatum, substantia nigra, pons, olives, Purkinje cells, vestibular and dorsal vagal nuclei and intermediolateral columns. Unfortunately it is not yet known whereabouts in the human medulla the relevant motor cells are to be found.

The practical management of these patients is extremely difficult. Clearly, when persistent nocturnal stridor occurs the upper airways obstruction may lead to hypoxia, and urgent but elective tracheostomy is required. However, this does not ensure the patients' safety in that apnœa and central disturbances of respiration may still occur despite the presence of the tracheostomy. Moreover, probably because of cardiac autonomic involvement, these patients are particularly liable to cardiac arrest, which appeared to be the final cause of death in all three patients.

SUMMARY

Clinical and pathological findings are reported in three cases of Shy-Drager syndrome with laryngeal stridor severe enough to require tracheostomy. Indirect laryngoscopy in all three cases revealed a failure to abduct the vocal cords properly with a resulting narrowing of the glottic airway. Histological studies showed a marked atrophy of the posterior crico-arytenoid muscles and little atrophy of the other laryngeal muscles. The posterior crico-arytenoid muscles have the sole responsibility of abducting the vocal cords, so it is concluded that the patient's stridor was caused by the selective paralysis of these muscles. Histological studies of the posterior crico-arytenoid muscles were suggestive of denervation but despite this finding, no clear evidence of any motor cell loss in the nuclei ambigui was obtained. Other possible causes of the selective posterior crico-arytenoid atrophy are discussed.

ACKNOWLEDGEMENTS

D.R.O. wishes to thank Mr Ron Beesley and Mr Rowland Cross for skilled technical help, and L.M. wishes to thank the staff of the Histopathology Department, Institute of Laryngology and Otology.

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(*Received December 2, 1980*)

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VISUAL EVOKED POTENTIALS ELICITED BY PATTERN REVERSAL DURING PROVOKED VISUAL IMPAIRMENT IN MULTIPLE SCLEROSIS

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INTRODUCTION

SOME patients with multiple sclerosis (MS) suffer from visual impairment of short duration in connection with physical effort. This symptom was first described in four such patients by Uhthoff in 1889. Since then, this phenomenon, now known as Uhthoff's symptom, has been repeatedly confirmed and extended. Thus, it is a well-known clinical observation that an increase in body temperature and emotional stress may also provoke transient reduction of vision in patients with MS (Brickner, 1950; McAlpine and Compston, 1952; Edmund and Fog, 1955; Ricklefs, 1961; Goldstein and Cogan, 1964; Thomson, 1966). In this regard, Perkin and Rose (1976) reported that 33 per cent of 125 MS patients investigated subserved Uhthoff's symptom, and 11 per cent experienced visual impairment by exercise.

The pathogenesis of Uhthoff's symptom is not fully understood. A critical reduction in the blood supply to the demyelinated optic nerve fibres has long been suggested as a possible cause (Franklin and Brickner, 1947; Brickner, 1950; Earl, 1964). Since many MS patients experience profound exacerbation of symptoms when raising their body temperature and the conduction of nerve impulses is blocked at a lower temperature in demyelinated nerves as compared with normal nerves (Davis, 1970; Davis and Jacobson, 1971; Rasminsky, 1973), it has been suggested that temperature is the main causative factor (*see* Halliday and McDonald, 1977). It cannot be excluded, however, that changes in the internal chemical environment (e.g., calcium-ions) may also contribute to the Uhthoff phenomen (Davis, Becker, Michael and Sorensen, 1970; Becker, Michael and Davis, 1974).

During the last decade, several investigators have shown that the visual evoked potentials (VEP) elicited by checkerboard pattern reversals are valuable in diagnosing demyelinating optic neuritis (Halliday, McDonald and Mushin, 1972, 1973*a*, *b*; Milner, Regan and Heron, 1974; Asselman, Chadwick and Marsden, 1975; Regan, Milner and Heron, 1976; Hennerici, Wenzel and Freund, 1977; Matthews, Small, Small and Pountney, 1977). During the time of visual impairment in the acute phase of the disease the amplitude of the pattern-reversal VEP is reduced, and returns to normal with clinical recovery, while the characteristically prolonged latency remains. Similar changes in pattern-reversal VEP may be expected to occur during the short-lasting visual impairment provoked by physical effort, increase in body temperature and emotional stress. The effect of body temperature elevation on critical flicker fusion (Namerow, 1971) visual perception (Galvin, Regan and Heron, 1976; Regan, Murray and Silver, 1977) visual (Regan *et al.*, 1977) and somatosensory evoked potentials (Matthews, Read and Pountney, 1979) has been studied in patients with MS. The results from these studies on VEP were, however, varied, since the patients were not selected with regard to the presence or absence of Uhthoff's symptom.

In a preliminary study (Persson and Sachs, 1978) we have reported that physical effort provoked visual impairment which was correlated with changes in the pattern-reversal VEP in two patients with MS. The present investigation was undertaken in order to further extend these results in a specially selected MS patient group with experience of Uhthoff's phenomenon compared with a MS patient group without such experience. Since lowering of body temperature and hyperventilation are procedures known to reduce symptoms and signs in MS (Watson, 1959; Michael and Davis, 1972), the additional effects of these procedures on the exercise-provoked visual impairment and VEP were also tested.

METHODS

Clinical Material

Fifteen patients, 25 to 56 years of age, with MS in a clinically stable phase of the disease, were included in this study. The diagnostic criteria for MS were those of McAlpine (1972) and the diagnosis was verified in 14 patients by the finding of MS-specific pattern on isoelectric focusing of the cerebrospinal fluid (Kjellin and Vesterberg, 1974). Eight of the patients had experience of visual impairment of short duration in connection with physical exercise (Uhthoff patients), whereas 7 had no such experience (non-Uhthoff patients). The effect of physical effort on VEP was tested on all 15 MS patients. Clinical data are summarized in Table 1. Twelve of the 15 patients (80 per cent) had a history of retrobulbar neuritis. Patient No. 1 denied such symptoms, but had experience of very severe bilateral Uhthoff's phenomenon which indeed was his first manifestation of MS. The time since the last exacerbation of MS symptoms did not differ between the Uhthoff (mean seven months) and the non-Uhthoff group (mean eight and a half months).

Control subjects were 5 healthy persons, 26 to 37 years of age, with no history of ophthalmological or neurological disease. Visual acuity was 1.0 (in one case after correction with glasses). In total, 10 normal eyes were tested.

Stimulation and Recording

Pattern-reversal stimulation was obtained with a commercially available TV-pattern-generator (Medelec Visual Stimulator, Arden, Faulkner and Mair, 1977). A black and white checkerboard pattern was presented on a standard 26 in TV set in front of the patient at a distance of 1.5 m. The whole

TABLE 1. CLINICAL MATERIAL, MS PATIENTS

Case no.	Age (yrs)	Sex	Retrobulbar neuritis		Central scotoma		Optic discs		General symptoms	Isoel. focusing on cerebrospinal fluid	Months since exacerbation
			R	L	R	L	R	L			
Uhthoff patients											
1	25	M	–	–	+	+	Pale	Pale	Transient ataxia	+	5
2	28	F	+	–	–	–	–	–	Sensory	+	2
3	31	F	–	+	+	+	Pale	Pale	Sensory	*	6
4	33	F	+	–	+	–	Pale	–	Sensory	+	4
5	35	F	+	–	+	–	Pale	–	Sensory and motor	+	3
6	35	M	+	+	+	+	Pale	–	Sensory	+	5
7	38	M	+	–	–	–	Pale	Pale	Sensory	+	23
8	50	F	–	–	–	+	–	–	Sensory and motor	+	9
Non-Uhthoff patients											
9	33	F	+	+	+	+	Pale	Pale	Sensory	+	9
10	35	F	+	+	+	+	Pale	Pale	Sensory and motor	+	3
11	35	M	–	+	–	–	–	–	Sensory	+	3
12	48	F	–	–	+	+	–	–	Sensory and motor	+	4
13	50	M	+	+	–	–	Pale	Pale	Sensory and motor	+	17
14	55	F	+	+	–	+	–	–	Sensory and motor	+	22
15	56	F	+	–	–	–	–	Pale	Sensory and motor	+	2

Nos. 1 to 8: Patients with MS experiencing transient decrease of vision on exercise. Nos. 9 to 15: Patients with MS not experiencing visual impairment on exercise. + = positive finding. – = negative finding. * = no information.

stimulating field corresponded to a visual angle of 15.2 deg and each square subtended a visual angle of 48 min of arc. The average luminance of the TV screen was 47 cd/m^2 with a contrast between squares of 50 per cent. Monocular stimulation of each eye was used with a pattern-reversal frequency of 2 Hz. The subjects were requested to fixate on a small spot of red light in the centre of the screen while the response was recorded. The VEPs were recorded between a mid-occipital electrode placed 5 cm above the inion (Oz) and a mid-frontal electrode (Fz). The occipital potentials were fed into a preamplifier with low and high frequency filters set at 0.8 and 80 Hz, respectively. VEPs to 128 reversals were averaged during 200 ms, using a Medelec DAV-6 averager, which was triggered by the pattern reversal.

The peak latency of the major positive wave of the VEPs was determined and its amplitude measured from the peak of the immediately preceding negativity. The latencies were measured with the strobe system of the DAV-6 unit on the averaged and amplified VEP presented on the oscilloscope. The amplitudes were measured from chart paper records.

Procedure

On the first day, pre-exercise VEPs were recorded during a recording session of 15 to 20 min and at least 6 VEPs were registered on stimulation of each eye. Visual acuity was measured with a Snellen chart. The body temperature was registered using a mouth thermometer. Thereafter, the subjects exercised on a bicycle ergometer for about 10 min with a load corresponding to 60 to 70 per cent of their maximal capacity. During the last minute of exercise, visual acuity and body temperature were again measured. The occurrence of nystagmus was looked for. The VEP recordings were continued during the following post-exercise period for 25 min which was until the responses had regained pre-exercise pattern. Control VEPs without provocation were recorded from 10 of the subjects on the next day.

In some of the subjects, additional tests were made with either hyperventilation or cooling of the legs in connection with the physical effort (3 Uhthoff patients—4 eyes; 2 non-Uhthoff patients—2 eyes; 2 normals—4 eyes). The subjects were instructed to hyperventilate maximally during the last 3 min of ergometer bicycling. For the cooling procedure, a device (Cryomat) was used in which cooled freon gas circulated in two systems of rubber tubings which formed flat cushions. These cooled cushions (outside temperature about 10° C) were completely wrapped around the thighs. During this cooling procedure the subjects reported a general feeling of cold and had a tendency to shiver. The cooling was started 30 min before and continued during the ergometer bicycling which was not restricted by the procedure. In all other respects, the additional tests were performed in the same way as described.

The study was approved by the Ethical Committee of the Karolinska Hospital.

RESULTS

A description of the clinical symptoms and signs of the 15 Uhthoff and non-Uhthoff patients examined in this study is provided in Table 1. The latency and amplitude values of the major positive component (P 100) of the VEP for these MS patients and the 5 normal controls are presented in Table 2. The visual acuity of each eye is also given. In a control group from our laboratory, which consisted of 17 healthy persons, 17 to 56 years of age, the mean latency to P 100 was 103 ms, SD ± 5 ms and the mean amplitude 7 μV, SD ± 2 μV. In this group, the variability of the latency and amplitude in consecutive recordings during one recording session lasting about 30 min was less than 5 ms and 30 per cent, respectively. The pre-exercise VEPs from the control subjects in the present study fell within this latency and amplitude range.

No VEP could be recorded from one eye in 2 patients (No. 6 and No. 9, visual acuity 0.1, respectively). Eight of the remaining 13 patients (62 per cent) had bilateral and 5 (38 per cent) unilateral prolonged latencies of the pre-exercise VEPs.

TABLE 2. VISUAL EVOKED POTENTIALS AND VISUAL ACUITY FINDINGS

Case no.	*Uhthoff*		*Pre-exercise visual acuity*		*Post-exercise visual acuity*		*Pre-exercise amplitude*		*Post-exercise amplitude*		*Pre-exercise latency*		*Post-exercise latency*	
	R	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*
Uhthoff patients														
1	+	+	1.0	1.0	0.4	0.5	5.1	3.8	0	2.2	**232**	**138**	–	141
2	+	–	1.0	1.0	0.4	1.0	6.2	6.4	0	5.7	**144**	99	–	95
3	–	+	1.0	1.0	1.0	0.3	7.4	8.5	8.0	5.0	103	**149**	104	174
4	+	–	0.8	1.0	0.6	1.0	5.2	11.1	3.0	10.8	**136**	100	134	99
5	+	–	1.0	1.0	0.8	1.0	10.1	11.4	4.0	10.3	**141**	**132**	139	133
6	*	+	0.1	0.9	–	0.7	–	7.7	–	3.0	–	**140**	–	141
7	+	–	1.0	1.0	0.4	1.0	5.0	5.6	0	6.3	**143**	**120**	–	120
8	+	–	0.7	1.0	0.4	1.0	8.4	5.8	3.0	...[1]	**131**	114	126	...[1]
Non-Uhthoff patients														
9	*	–	0.1	0.5	0.1	0.6	–	3.4	–	2.2	–	**165**	–	166
10	–	–	0.5	0.6	0.6	0.6	6.8	5.1	5.2	6.7	**133**	**129**	128	130
11	–	–	0.9	1.0	0.9	0.9	10.8	7.2	11.5	6.0	108	**164**	106	162
12	–	–	0.8	1.0	0.7	1.0	8.7	5.7	7.4	4.7	**142**	**130**	140	130
13	–	–	1.0	1.0	1.0	1.0	8.9	9.3	8.3	8.7	**168**	**170**	170	170
14	–	–	1.0	0.7	1.0	0.6	4.9	4.5	4.9	4.7	112	**137**	108	132
15	–	–	0.5	0.9	0.5	0.9	2.4	3.1	4.6	3.2	**154**	**149**	151	150
Normals														
16	–	–	1.0	1.0	1.0	1.0	6.6	5.6	7.7	6.3	102	103	102	103
17	–	–	1.0	1.0	1.0	1.0	5.7	5.3	6 2	7.0	92	92	88	91
18	–	–	1.0	1.0	1.0	1.0	8.3	9.2	8.7	7.0	98	98	97	96
19	–	–	1.0	1.0	1.0	1.0	4.8	5.3	3.2	5.0	93	94	93	94
20	–	–	1 0	1.0	1.0	1.0	7.9	6.8	10.7	7.2	100	102	99	99

+ = positive finding. – = negative finding * = no VEPs recorded. Abnormal VEP latency findings in pre-exercise recordings are indicated in bold type. [1] This eye was not tested.

The mean latency of these delayed VEPs in the Uhthoff group (N = 9, mean 150.4 ms, SD ± 31.0 ms) did not differ from that of the non-Uhthoff group (N = 11, mean 149.2 ms, SD ± 16.0 ms). The amplitudes of the pre-exercise VEPs in all subjects ranged from 2.4 to 11.4 μV and the mean values of the delayed VEPs were similar in the Uhthoff (N = 9, mean 6.7 μV, SD ± 2.1 μV) and the non-Uhthoff groups (N = 11, mean 5.9 μV, SD ± 2.4 μV). The visual acuity varied from 0.5 to 1.0 in the eyes of the MS patients from which VEP could be elicited.

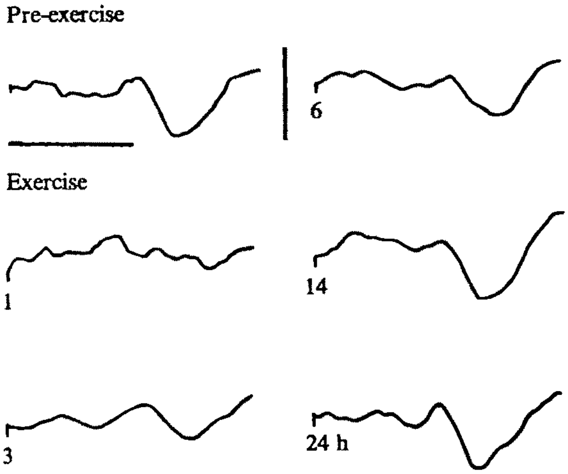

FIG. 1. The effect of physical exercise on VEP of a patient with MS with Uhthoff's symptom (No. 2). The amplitude is reduced without change in the prolonged latency. The numbers below each response represent time after exercise in minutes except for 24 hours (h). Horizontal bar = 100 ms; vertical bar = 10 μV.

The qualitative changes in VEP provoked by exercise in one MS patient (No. 2) with experience of Uhthoff's symptom are shown in fig. 1. The pre-exercise VEP had a markedly prolonged latency with an amplitude within the above-mentioned range. Thus, the VEP pattern was typical, although not specific, for demyelinating optic neuritis. Ten minutes of exercise on the bicycle ergometer provoked a visual impairment and a marked reduction of the VEP amplitude but no change in the P 100 latency. Nystagmus was not observed in this patient or in any of the subjects examined. This pattern, with a solitary short-lasting reduction in amplitude of the VEPs after exercise was typical for the patients with Uhthoff's symptom, although the degree of reduction varied. Fig. 2 shows the VEPs before and after exercise in one MS patient (No. 13) without experience of Uhthoff's symptom. The provocation did not reduce the visual acuity. No changes could be seen in the characteristically prolonged latency of P 100 or in the amplitude of the VEP. In fig. 3, it can be seen that the latency and amplitude of the VEP in one normal person (No. 17) did not change during the provocation test. The subject reported no alteration in visual acuity.

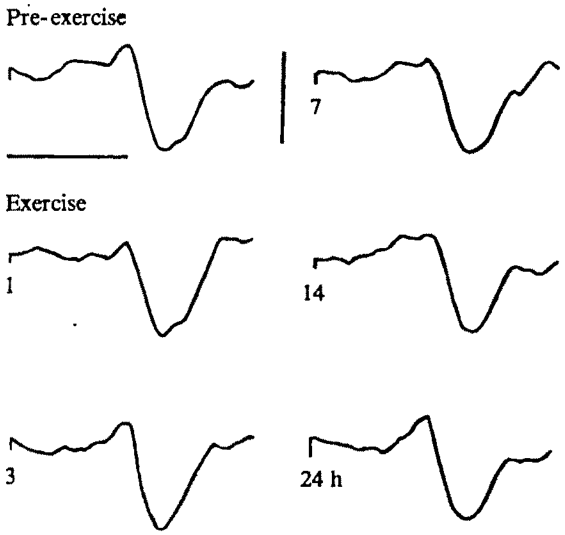

FIG. 2. VEP before and after physical exercise in a non-Uhthoff patient with MS (No. 13) showing no change in either the amplitude or the prolonged latency. The numbers below each response represent time after exercise in minutes except for 24 hours (h). Horizontal bar = 100 ms; vertical bar = 10 μV.

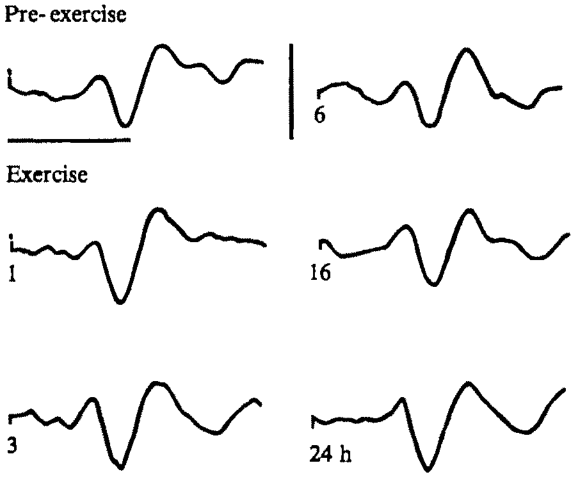

FIG. 3. VEP before and after physical exercise in a normal person (No. 17) showing no change. The numbers below each response represent time after exercise in minutes except for 24 hours (h). Horizontal bar = 100 ms; vertical bar = 10 μV.

TABLE 3. CHANGES IN MEAN VALUES AND SD OF VISUAL ACUITY, RELATIVE AMPLITUDE AND LATENCY PROVOKED BY EXERCISE

	Visual acuity	*Relative amplitude*	*Latency*
Uhthoff patients	−0.4±0.2	−68±26	3.3±11.5 (N = 6)[1]
Non-Uhthoff patients	−0.01±0.07	2±33	1.1±2.8
Normals	0±0	5±22	−1.2±1.4

[1] No VEP was recorded after exercise in 3 of the 9 Uhthoff eyes.

The changes provoked by exercise in visual acuity, relative amplitude and latency of the P 100 component in Uhthoff and non-Uhthoff patients, as well as normals, are given in Table 2 for single eyes and in Table 3 for mean values and SD of each group, respectively. In none of the groups did exercise alter the mean latency to P 100. The variability in latency was most pronounced in the Uhthoff group. This variability can be explained by the fact that in one Uhthoff patient (No. 3) a large increase in latency (25 ms) was noted after exercise. The change may be due to unmasking of a VEP component not observed earlier and not represent a true latency prolongation. The effect of exercise on the latency to P 100 in the remaining Uhthoff patients (N = 5) did not differ from the normals. The mean VEP amplitudes in the non-Uhthoff and the normal groups were not influenced by physical exercise. In one non-Uhthoff patient (No. 9) and one normal subject (No. 19), amplitude reductions of 35 per cent and 33 per cent respectively, slightly larger than our normal range (< 30 per cent) were observed. On the other hand, a large increase was registered from one non-Uhthoff patient (No. 15; 92 per cent) and one normal subject (No. 20; 35 per cent). Exercise had no effect on the visual acuity of the non-Uhthoff patients and normals.

The magnitude of the provoked reduction in visual acuity and VEP in the Uhthoff group differed between the subjects. The mean value of the change in visual acuity was 0.4, range 0.2 to 0.7 and the decrease in mean amplitude amounted to 70 per cent, range 40 to 100 per cent (Tables 3 and 4). Generally, greater reduction in

TABLE 4. RELATIONSHIP BETWEEN VARIOUS PARAMETERS IN THE UHTHOFF GROUP AND THE PROVOKED VISUAL IMPAIRMENT

Patient no.	*4*		*5*		*6*		*8*		*1*		*2*		*7*		*3*	
	R	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*
Uhthoff's symptom	+	−	+	−	*	+	+	−	+	+	+	−	+	−	−	+
Change in visual acuity	−0.2	−	−0.2	−	*	−0.2	−0.3	−	−0.5	−0.6	−0.6	−	−0.6	−	−	−0.7
Relative VEP amplitude change	−42	−	−60	−	*	−61	−65	−	−42	−100	−100	−	−100	−	−	−41
Pre-exercise latency	**136**	100	**141**	**132**	*	**140**	131	**114**	**232**	**138**	**144**	99	**143**	**120**	103	**149**
Pre-exercise amplitude	5.2	11.1	10.1	11.4	*	7.7	8.4	5.8	5.1	3.8	6.2	6.4	5.0	5.6	7.4	8.5
Time since retrobulbar neuritis (month)	4		3		5		9		5		2		23		6	
Change in oral temperature	−0.6		0		+0.5		+0.1		0		0		+0.3		+0.2	

+ = positive finding. − = negative finding. * = no information. Abnormal VEP latency findings in pre-exercise recordings are indicated in bold type. The patients are arranged according to the degree of provoked reduction in visual acuity.

amplitude was related to greater decrease in visual acuity. It can be seen in fig. 4, which shows the time-course of the VEP amplitude change after physical exercise, that the VEP reduction had a duration of about 10 min. Most of the patients reported a return of normal vision after about 7 to 8 min, when the VEP amplitudes corresponded to the lower end of the pre-exercise amplitude range.

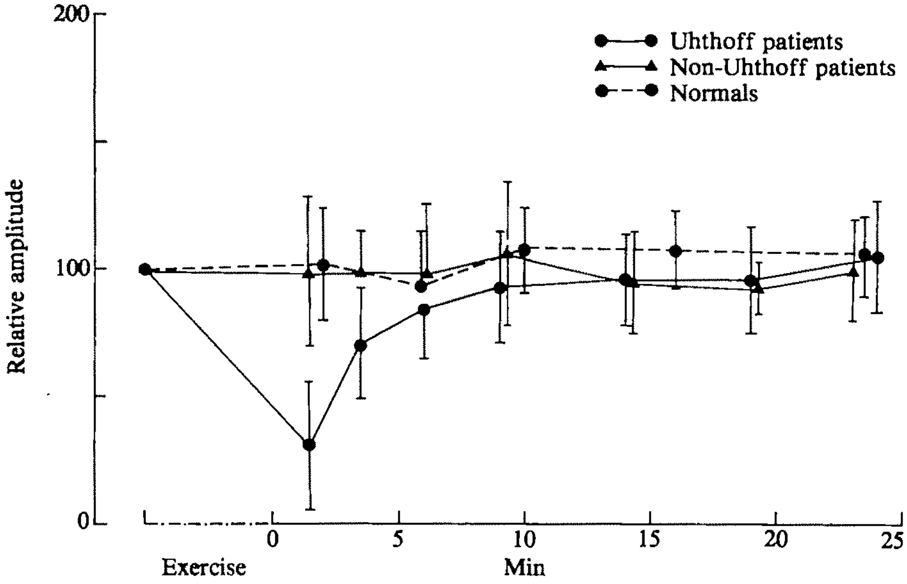

FIG. 4. Changes with time after exercise in mean relative VEP amplitude ±SD in the three groups examined. 100 represents the mean amplitude value of each VEP obtained at the pre-exercise control recordings. Short-lasting VEP amplitude reduction was observed in the Uhthoff group compared to no change in the other groups.

In patients with unilateral Uhthoff's symptom, normal VEPs were recorded in 3 and abnormally delayed VEPs in 3 subjects from the eyes not showing the symptom. These VEPs (one eye not tested, Patient No. 8) showed no change with physical exercise. Unilateral Uhthoff's symptom appeared on the side from which the largest latency prolongation was recorded. In the case with bilateral symptoms, the VEP with the largest latency prolongation showed the greatest amplitude reduction. No consistent relationship was found in the Uhthoff group between the degree of provoked visual impairment and the amplitude of the pre-exercise VEPs or the time since the last exacerbation of acute optic neuritis (Table 4). Three of the Uhthoff patients have been re-examined six to twelve months after the first test. Provocation with physical exercise had less marked effect on the VEP amplitude in two of them (Nos. 5 and 6) but more pronounced effect in the third patient (No. 1).

The body temperature was measured orally before and after exercise in all subjects examined. The mean temperature increased slightly in all groups (Uhthoff group, +0.1° C; non-Uhthoff group, +0.2° C; normal group: +0.5° C). No clear relationship was observed between the changes in oral temperature and VEP amplitude in the Uhthoff group (Table 4). Although the cooling procedure produced a sensation of chill in all subjects, it did not prevent an increase in mean oral temperature in normals (+0.4° C) during exercise. Cooling did, however, reduce slightly the mean temperature in the Uhthoff (−0.1° C) and non-Uhthoff groups (−0.2° C). Cooling or hyperventilation had no additional effect on the VEP.

The VEPs recorded in the subjects on the next day did not differ from the pre-exercise controls.

DISCUSSION

The present results show that the amplitude of the pattern-reversal VEP was reduced during the short-lasting visual impairment which was provoked by physical effort in MS patients selected on the basis of a history of Uhthoff's symptom. The changes were related to a reduction in visual acuity. In most patients, exercise provoked only unilateral changes in VEP and visual acuity which seemed to be related to the P 100 latency (*vide infra*), but not to the amplitude of the pre-exercise VEPs. There was no relationship between the presence of Uhthoff's symptom and the length of time passed since the last exacerbation of acute optic neuritis. The characteristically prolonged P 100 latency was not significantly changed. The same physical effort causing visual impairment in Uhthoff patients, did not influence the VEP or visual acuity either in MS patients without Uhthoff's symptom or in normal subjects.

Since the observed VEP amplitude reduction was unilateral in all cases but one, it is unlikely that it is due to lack of fixation of the TV pattern. Moreover, nystagmus was looked for and not observed. Impaired recording conditions (electrode failure etc.) with passage of time cannot explain the changes, since they were unilateral and not recorded in pre-exercise control registration of the same length of time. The degree of physical effort may of course influence the results, but then inadequate provocation should give negative results, and hence not cause VEP changes. The amplitude reductions of the VEP is therefore in all probability provoked by the physical effort.

In the present study the MS patients comprising the Uhthoff group were selected with a history of exercise-provoked visual impairment and the non-Uhthoff patients without a history of such symptoms. All Uhthoff patients showed varying degree of VEP amplitude reduction on physical exercise but no non-Uhthoff patients. In recent studies, it was reported that elevation of body temperature provoked VEP changes in some only of the MS patients (Regan *et al.*, 1977, Matthews *et al.*, 1979). These patients were not selected on the basis of presence or absence of temperature-induced visual impairment and would therefore correspond to both groups of MS patients in the present study. Hence, it is to be expected that not all of these MS patients showed VEP changes on temperature provocation.

Matthews *et al.* (1979) also found a significant reduction in VEP amplitude on elevation of body temperature in healthy control subjects. It is remarkable that this amplitude change was not related to a reduction in visual acuity. Furthermore, there was no significant effect of temperature on the somatosensory evoked potential amplitude, which in this case makes a general temperature-mediated influence on the nerve impulse transmission less likely. In our study exercise-provocation had no effect on the VEP amplitude and visual acuity in normal subjects.

Demyelination of nerve fibres is considered to be associated with three main impulse conduction defects: slowing of conduction velocity; conduction block and/or inability to transmit high frequency trains of impulses (*see* McDonald, 1974). It has been suggested that visual impairment and VEP amplitude reduction during the acute phase of demyelinating optic neuritis is due to a reversible block in the conduction of impulses in the optic nerve fibres (Halliday and McDonald, 1977; *see also* Halliday *et al.*, 1972, 1973*a*, *b*). Such a conduction block may also explain the present findings in the Uhthoff patients. The likelihood that a conduction block plays a causative role in Uhthoff symptomatology rather than a reduction in conduction velocity is supported by the observation that the VEP latency did not change significantly in these patients. Furthermore, most of the clinical symptoms and signs in MS are due to loss of function and considered to be related to such a conduction block.

Perkin and Rose (1976) found no correlation between the development of Uhthoff's symptom and the parameters of optic nerve function studied. Similarly, no consistent relationship could be observed in the present study between, on the one hand, the amplitude of pre-exercise control VEPs, the time since last exacerbation of acute optic neuritis and on the other, presence of provoked visual impairment and VEP changes. However, it is obvious that prolongation of VEP latency indicating optic nerve demyelination is a prerequisite for Uhthoff's symptom. The pre-exercise control VEPs from Uhthoff eyes all had longer VEP delays than the opposite eyes without the symptom. Also, in the case with bilateral symptoms, the VEP with the largest latency delay showed the greatest amplitude reduction. These observations support the supposition that more extensive MS plaques of the optic nerve (causing larger VEP delays) are more likely to produce a failure of nerve impulse transmission and a conduction block on provocation, thus giving rise to the symptom. By analogy, it has been shown experimentally that large demyelinating lesions of nerve fibres produce conduction block, but with smaller lesions conduction can continue (McDonald and Sears, 1970). This cannot, however, be the sole explanation why some demyelinating optic nerve fibres are blocked by provocation but others not, since the VEP delays in the Uhthoff and the non-Uhthoff group were of the same order of magnitude.

Different pathophysiological mechanisms have been proposed for the presumed conduction block responsible for Uhthoff's symptom, such as changes in blood circulation, temperature and/or the internal chemical milieu. It has been suggested that physical exercise reduces local blood flow below a critical level in the demyelinated nerves (Franklin and Brickner, 1947; Brickner, 1950; Earl, 1964). In one of our patients with very severe bilateral Uhthoff's symptom (No. 1) an orbital phlebogram was normal and treatment with an alpha-receptor blocking drug azapetine phosphate (Ilidar, Roche) had no effect on the symptoms.

Hyperventilation and intravenous injection of sodium bicarbonate or disodium edetate (Na_2 EDTA), procedures believed to produce a decrease in serum ionized calcium, have been shown to improve symptoms and signs in MS (Davis *et al.*, 1970; Becker *et al.*, 1974). In the present study, hyperventilation did not decrease the exercise-induced VEP amplitude reduction. This may have been due to inadequate hyperventilation.

It has been shown repeatedly in animal experiments that the temperature threshold for conduction block is lower in demyelinated nerve fibres than in normal fibres (Davis, 1970; Rasminsky, 1973). Many MS patients experience profound exacerbation of their symptoms in connection with hot baths and this sensitivity to temperature elevation may be such that even the circadian fluctuations in temperature have been reported to produce visual changes in one MS patient (Namerow, 1968). Thus, an increased temperature due to exercise may be a direct cause of the VEP-related visual impairment. Raising body temperature has been described to cause an increase in VEP delays in 2 of 4 MS patients (Regan *et al.*, 1977) and reduced VEP amplitudes in MS patients and normals (Matthews *et al.*, 1979). In the present study the mean mouth temperature was increased to the same order of magnitude both in the Uhthoff and the non-Uhthoff groups and was not related to the provoked VEP changes. However, oral temperature measurements are not reliable during physical exercise but there is no other convenient method known of central temperature registration under such conditions (Nadel, 1977). Thus, the observed lack of correlation between temperature and VEP alterations does not exclude the possibility of a temperature-mediated effect. It is obvious that the present results cannot settle the question of which pathophysiological mechanisms cause the provoked visual impairment.

In follow-up tests of 3 Uhthoff patients 2 showed less marked effects on the VEP amplitude after ergometer cycling and one a more pronounced effect. Negative effects may be due to inadequate physical effort, but could be due to fluctuations in sensitivity to provocation with time. In this context it may be mentioned that one MS patient tested with repeated hyperthermia over a four-and-a-half-month period showed fluctuations in temperature sensitivity (Michael and Davis, 1972).

It is notable that physical exercise combined with VEP registration is a sensitive procedure to demonstrate objectively-provoked visual impairment in MS patients with a history of Uhthoff's symptom. Such investigations could therefore be clinically helpful in differentiating Uhthoff's symptom from other causes of amaurosis fugax.

SUMMARY

Many patients with multiple sclerosis suffer from a visual impairment of short duration in connection with physical effort, raised body temperature, emotional stress and other provocations (Uhthoff's symptom). The effects of physical exercise on the pattern-reversal visual evoked potential were studied in patients with multiple sclerosis, with and without a history of Uhthoff's symptom, and in normals. Physical effort provoked a short-lasting reduction in the amplitude of the visual evoked potential and in the visual acuity of patients with multiple sclerosis with a history of Uhthoff's symptom. No significant change was observed in the characteristically prolonged latency of the visual evoked potential. Provocation with the same physical effort did not significantly influence the visual evoked potential and visual acuity in patients with multiple sclerosis but without Uhthoff's sympton, or in normals. It is suggested that the cause of Uhthoff's symptom is a reversible conduction block in impulse transmission by the demyelinated optic nerve fibres.

ACKNOWLEDGEMENTS

This study was supported by grants from the Karolinska Institute and the Swedish Multiple Sclerosis Foundation. We are grateful for the technical assistance of Ann Tiselius.

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(*Received October 21, 1980*)

Brain (1981), **104**, 383-404

THE RESTORATION OF CONDUCTION BY CENTRAL REMYELINATION

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INTRODUCTION

ONE of the remarkable characteristics of the symptoms produced by demyelinating lesions of the central nervous system is their tendency to remit. The mechanism of remission is, however, poorly understood. It has long been known that peripheral demyelinated fibres can be repaired by remyelination and that conduction block is relieved as the new myelin sheaths are formed (Denny-Brown and Brenner, 1944*a*, *b*; Kaeser, 1962; Morgan-Hughes, 1968; Ochoa, Fowler and Gilliatt, 1972). It is now known that remyelination can occur on demyelinated central nerve fibres including those in the plaque of multiple sclerosis (Bunge, 1968; Prineas and Connell, 1979) and it has been suggested that as in the peripheral nervous system, recovery of function may be influenced by it. There are, however, a number of differences between the newly formed sheaths of the central and peripheral nervous systems. In contrast to the fairly uniform length of peripheral remyelinated internodes (approximately 300 μm) those on central nerve fibres range from the very short (less than 10 μm) to within the normal range (Gledhill, Harrison and McDonald, 1973; Blakemore, 1974; Gledhill and McDonald, 1977; Clifford-Jones, Landon and McDonald, 1980; Blakemore and Murray, 1981). Because of these differences and those in the structural organization of normal central tracts and peripheral nerve, it is impossible to predict with confidence whether the newly formed central nodes would be functional or whether the conductive and capacitative current losses across long, thin remyelinated internodes would be too great for the remyelinated fibres to conduct trains of impulses securely. A previous investigation was inconclusive (Mayer, 1971) and so we have made a serial study of the changes in conduction occurring during demyelination and remyelination in the lesion produced by the direct micro-injection of lysophosphatidyl choline (LPC) into the spinal cord (Blakemore, Eames, Smith and McDonald, 1977). A short account of the present work has been published (Smith, Blakemore and McDonald, 1979).

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METHODS

Five cats were used. During all implantation, intraspinal injection and recording procedures, the cats were anæsthetized (Saffan, Glaxo) following premedication with atropine sulphate (400 μg/m). The rectal temperature was routinely monitored and maintained at 37° C using a homœothermic blanket. All surgical procedures were performed with aseptic precautions.

Implantation

Two methods of implantation were used. In two animals (SC61 and SC63) the T13 and L4 laminæ were exposed, cleaned and sufficient bone drilled away from the dorsal arch to permit the insertion of a pair of stimulating electrodes. The electrodes consisted of platinum discs embedded in small sheets of silicone rubber (Dow Corning, design developed by Dr R. G. Heath, Tulane University). The electrodes were positioned extradurally and fixed in position with dental cement which was in turn anchored around stainless steel screws fixed in the dorsal spinous process. The wires from the two implants were channelled subcutaneously to the head and soldered to four sockets of a miniature 9 socket plug (adapted from 'Radiospares' miniature plug). Other sockets were connected to stainless steel screws fixed through the skull. These screws served as EEG and earth electrodes and also provided anchorage for the dental cement around the plug. The scalp was drawn up around the implant.

In the three remaining animals (SC70, SC72 and SC80) laminæ at L1 and L3 were exposed and two holes, 6 mm apart, were drilled in the dorsal arch to admit two electrodes (stainless steel watchmakers screws) which were positioned so that they ended flush with the ventral surface of the arch. The electrodes were connected *via* short wires to stout (2 mm diameter) silver-coated brass poles which protruded through the skin when positioned in the implant. These poles were insulated from the surrounding tissues by silicone rubber sleeves. Anchoring stainless steel screws were placed in the dorsal spinous process and the electrodes and poles were securely cemented in position. The skin and paravertebral muscles were drawn closely around the implant.

Injection of LPC

Cats received LPC injections when recordings had been stable on at least three successive occasions over a period of one to two months.

A hemilaminectomy was performed between the two previously implanted laminæ. The spinous process of the lamina was fixed rigidly by a clamp to reduce reflex cord movements. Small holes were made in the dura over the regions of the dorsal column reported to contain the central projections of the saphenous nerve fibres (Liu, 1956; Imai, 1964). Up to four injections (each of 1.5 to 2.0 μl) of 0.8 per cent LPC in saline (Sigma Chemicals) about 2 to 3 mm apart, were made into each dorsal column using a micropipette attached to an Agla micrometer syringe (Welcome Reagents Ltd). The dura was left open and the wound closed in layers. All animals were given procaine penicillin post-operatively.

Behavioural Testing

The cats were examined for any deficit following implantation and LPC injection by assessing their hopping, tactile placing, pinch withdrawal and avoiding reactions (*see* Bard, 1933; Denny-Brown, 1966).

Serial Recording

Serial recordings were made both before and after the induction of the lesions but no recordings were made during the one to two months directly following implantation. The recording regime was the same on each occasion.

The animal was anæsthetized and laid supine to bring the dorsal columns into closer contact with the implanted electrodes. The rectal temperature was monitored using an electrical thermometer (Lightfoot) and care was taken to maintain it at 37 ± 0.5° C with a homœothermic blanket during the recording session. The cat was intubated and the expired CO_2 level continuously monitored using an infra-red CO_2 analyser (Capnograph) and a calibrated Y,t recorder. Paralysis was induced with intravenous gallamine triethiodide (Flaxedil, May and Baker) and the cats were artificially ventilated with oxygen-enriched air to maintain the end-tidal CO_2 level at 4 to 5 per cent. The EEG was routinely displayed and used to monitor the depth of anæsthesia during paralysis. Following the recordings the paralysis was reversed with intravenous neostigmine (Roche) and anæsthesia discontinued.

The implanted spinal electrodes were used for stimulation and were connected either to an isolated stimulator (Devices DS2) or to earth. Recordings were made from each saphenous nerve by placing a subcutaneous needle electrode close to it and recording against an indifferent 1.5 cm away in muscle. Constancy of electrode position at different recording sessions was ensured by tattoo marks placed in the skin. Differential recordings of the evoked nerve action potentials were made *via* unity-gain cathode followers. The over-all time constant of the recording and averaging apparatus was one second and a high frequency filter of 10 kHz was applied at the pre-amplifier stage.

At the beginning of each recording session the caudal implanted electrodes were earthed and the stimulus threshold at the rostral site was determined for each saphenous nerve. The averaged responses ($n = 64$) to stimuli of 2, 3, 4 and 6 times threshold were obtained for each leg. Although it is possible that the apparent threshold at the rostral stimulating site could be influenced by the number of fibres conducting, this problem did not affect the present results since a constant threshold relationship was established between the right and left saphenous nerves in all cats during the pre-lesion period. Thresholds for each leg were usually the same. Since the lesion placement only affected significantly the recordings from one leg, a clear threshold determination was possible on each occasion and this was used for determining the stimulus strength for both sides. The pre-lesion threshold relationship was always re-established when the responses obtained through the lesion were of sufficient amplitude to be observed clearly. The stimulus threshold (approximately 2 to 3 volts at 0.1 ms duration) either remained relatively constant over the months or showed a small increase (of about 75 per cent overall) with time. It is likely that such increments in threshold reflected the slow accumulation of fibrous tissue observed over those implanted electrodes which ended short of the spinal canal.

The ability of the fibres to conduct closely spaced action potentials was determined by using a series of paired stimuli having a range of interstimulus intervals. A specially constructed circuit (*see* Smith, 1979) enabled the response to the first stimulus of the pair to be subtracted from the records and it was thus possible to determine the refractory period of transmission (RPT) of the fibres (McDonald and Sears, 1970), that is, the minimum interval between two impulses at which the second impulse just failed to be conducted across the lesion.

The recording procedure was then repeated, earthing the rostral electrodes and stimulating at the caudal site. Occlusion of the response from the rostral electrodes as the stimulus strength at the caudal site was increased established that the fibres contributing to the caudal (control) responses included those stimulated at the rostral site.

Although the dorsal root reflex (*see* Casey and Oakley, 1972) was not prominent in the present experiments, the latency of the resulting impulses is such that they might be confused with direct conduction delayed by demyelination. For this reason a conditioning shock preceded every averaged record by 20 to 30 ms in order to render the dorsal root reflex refractory. This interval was chosen after measurements of the duration of the refractory period of the dorsal root reflex in acute experiments on normal animals.

Mapping the Location of the Saphenous Fibres

The actual location of the saphenous fibres in the dorsal columns was mapped physiologically (*see below*) and this map was later compared with a histological map showing the extent of the lesion.

In terminal experiments relaxant anæsthesia was used as before. The two saphenous nerves were dissected free and raised upon recording electrodes. A laminectomy from the level of the lesion to L7 was performed and the dura opened under paraffin. A focal anode was placed on the dorsal column just rostral to the lesion and the stimulating cathode was connected to a saline-filled micropipette positioned just caudal to the anode and held in a micro-manipulator. This cathode was sequentially positioned at each point of a quarter-millimetre grid across and into the dorsal column. At each position the threshold stimulus current necessary to excite three saphenous units was determined; three units were chosen in order to minimize the risk of underestimating the threshold if the cathode happened to be close to a node. The stimulus currents were plotted against the grid co-ordinates to provide a contour map of the threshold distribution across the dorsal column. The contours of lowest threshold indicated the location of the saphenous fibres.

Perfusion

The cats were perfused with glutaraldehyde (4 per cent in phosphate buffer, pH 7.2 to 7.4) and the lesion was cut into transverse blocks. After post-fixation in osmium tetroxide (1 per cent) and dehydration with graded ethanols the blocks were embedded in Araldite and sections taken for light and electron microscopy. Tracings of photomicrographs of these sections were superimposed to prepare a map showing the extent and location of the lesion in each animal.

RESULTS

Histology

A full account of the lesion produced by the injection of LPC into the cat spinal cord has been given elsewhere (Blakemore *et al.*, 1977). Here we describe only the main features of the lesion relevant to the interpretation of the physiological results.

The lesions were well-circumscribed and situated in the dorsal columns (fig. 1).

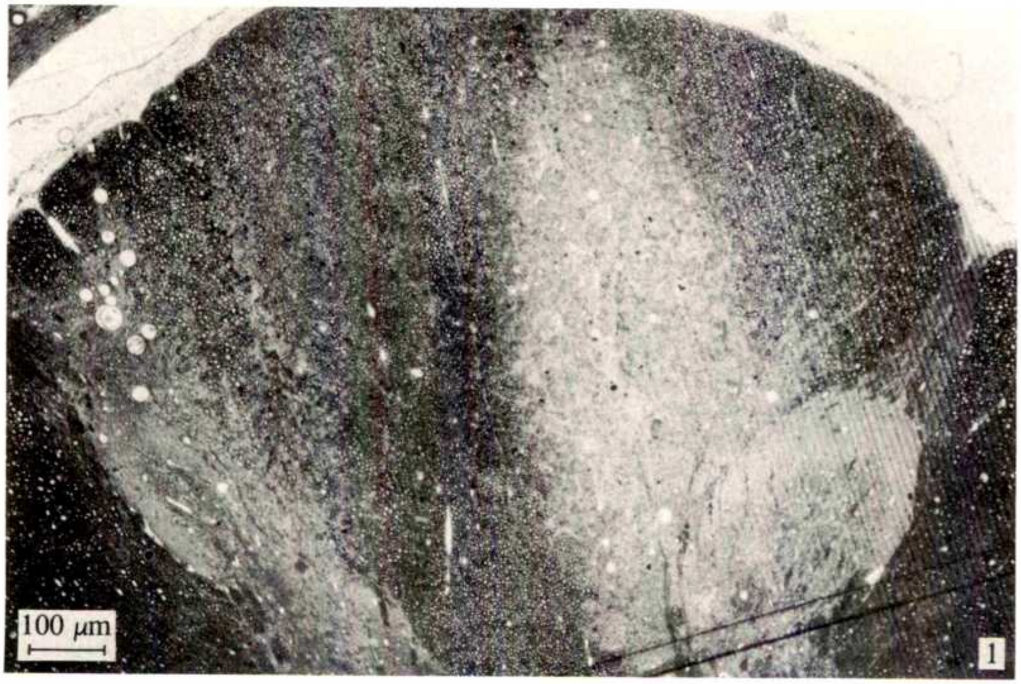


FIG. 1. Area of demyelination in the dorsal columns induced by injection of 2 μl of LPC. Toluidine blue.

Each injection produced primary demyelination for 2 to 5 mm along the length of the cord, covering approximately 1.5 mm^2 in transverse section. Some axonal degeneration was present, mainly at the centre, in all lesions.

Three days after LPC injection most fibres were demyelinated and some were completely demyelinated. The usual pattern of myelin breakdown involved splitting of the intraperiod line. The œdema present soon after the injection resolved during the first week.

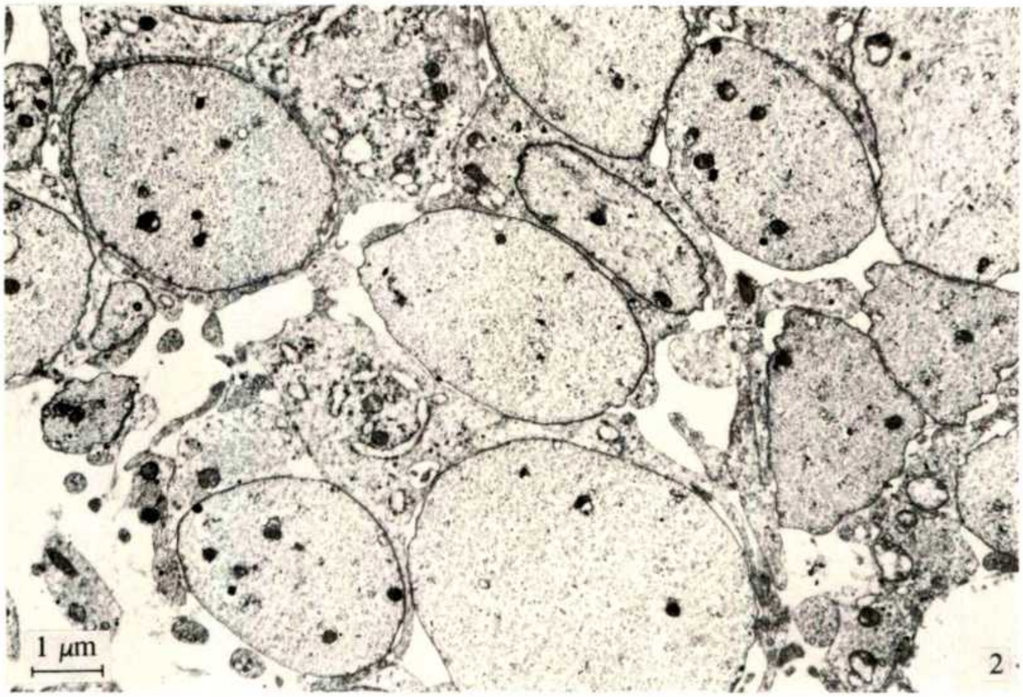


FIG. 2. Eight-day lesion. Note that demyelinated axons are associated with cellular processes.

At seven days the fibres within the lesion were demyelinated. The fibres either lay free in the extracellular space or were partially or completely surrounded by glial cell cytoplasm (figs. 2 and 3). There were many debris-filled macrophages. The classification of individual glial cells was often difficult but some could be identified as astrocytes and others as oligodendrocytes or Schwann cells.

Between seven and ten days, demylinated axons became increasingly associated with glial cells (fig. 3) and by ten to fourteen days the first axons to be remyelinated were invested with two to three lamellæ of compact myelin.

By one month many remyelinated axons were present in the lesion. A few axons, especially those near blood vessels and in the centre of the lesion, were remyelinated by Schwann cells but the majority were remyelinated by oligodendrocytes. A few demyelinated axons associated with astrocytes were still present (fig. 4).

Two months after LPC injection there were virtually no demyelinated axons, that is, the surviving affected fibres were remyelinated. Longitudinal sections at this stage revealed that some of the remyelinated internodes were short (down to 16 μm) and a few fibres possessed chains of short internodes. Other internodes were of indeterminate length but node frequency was greater than normal.

Examination of teased fibres (Blakemore and Murray, 1981) revealed that although the length of the remyelinated internodes was in general shorter than normal, it often fell within the normal range.

Three months after injection the remyelinated sheaths were thicker than at two months and little myelin debris was present. Subsequent changes in the affected fibres were small.

There was no evidence of axonal regeneration.

The spinal cord beneath the electrode implants was examined histologically in each preparation. Although in some preparations the profile of the dorsal columns showed a small irregularity produced by the presence in the spinal canal of the electrode, there was usually no damage to the cord itself. In some other animals a few superficially placed fibres showed degenerative changes.

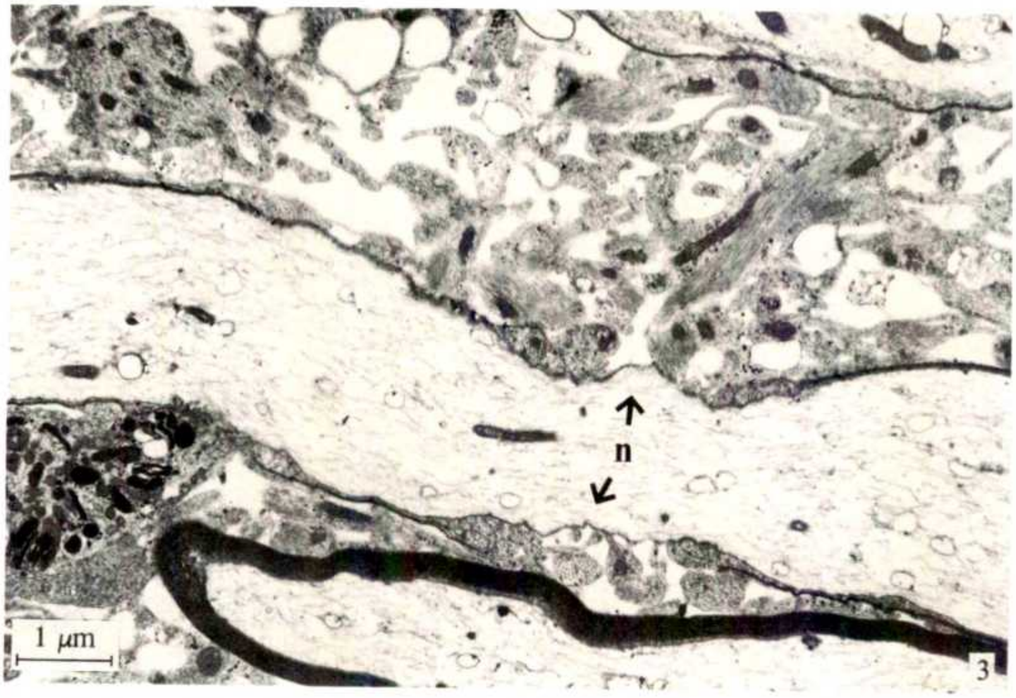


FIG. 3. Eleven-day lesion. An axon is covered by a thin layer of myelin. A node is present at n.

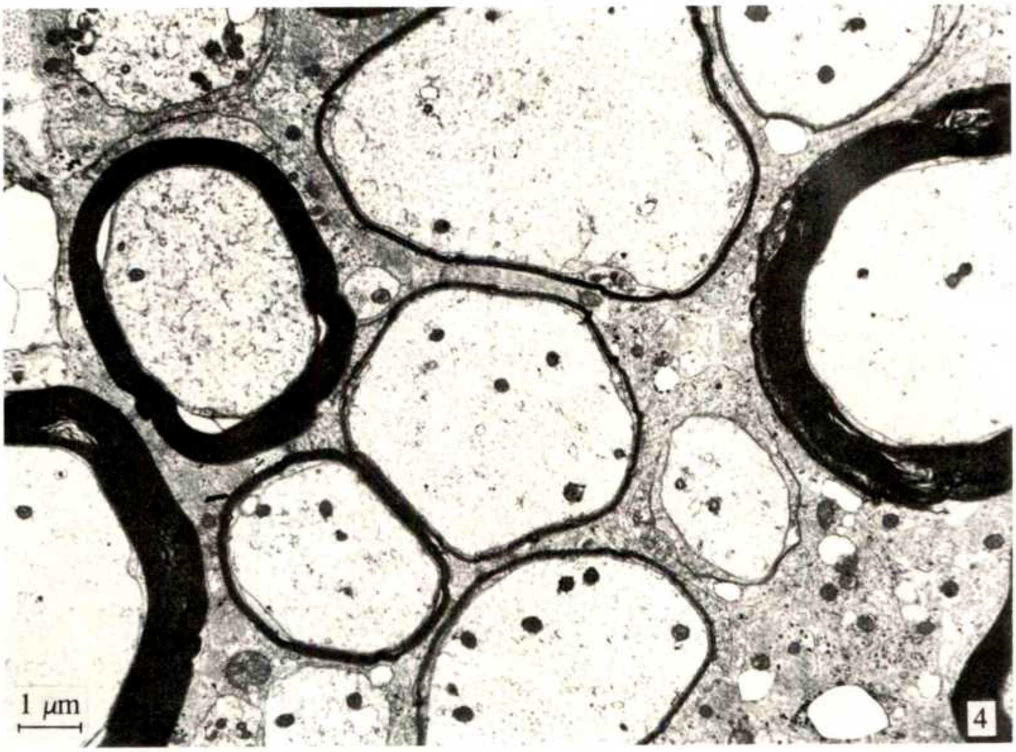


FIG. 4. One month lesion. Most of the axons are thinly remyelinated but a few demyelinated axons and some normally myelinated axons are also visible.

Behavioural Examination

The cats were assessed behaviourally following implantation and induction of the lesion but none had any deficit revealed by the tests employed.

Physiological Changes

Both implantation techniques gave consistent recordings for periods of at least a year.

Serial recordings from cat SC79 are illustrated in fig. 5. Similar results were obtained from the other animals (*see*, for example, the data from SC63 in fig. 9A). The responses obtained by stimulation at the rostral site before the lesion was induced are relatively constant showing that for the control period of a month or so the recordings were quite stable. However, a marked change in the responses was observed three and seven days after the lesion was induced. On these days the compound action potential was markedly reduced in amplitude. No increase in the number of more slowly conducting fibres was detected even by prolonged averaging with a long sweep duration. These observations suggest that conduction block had developed in many fibres and this interpretation was confirmed by the observation of a large positivity in antidromic recordings made acutely at the lesion site after seven days (fig. 6).

In one cat (SC79) a series of recordings was made at seven days both before and after administering Flaxedil. Apart from abolishing the EMG the Flaxedil had no effect upon the recordings.

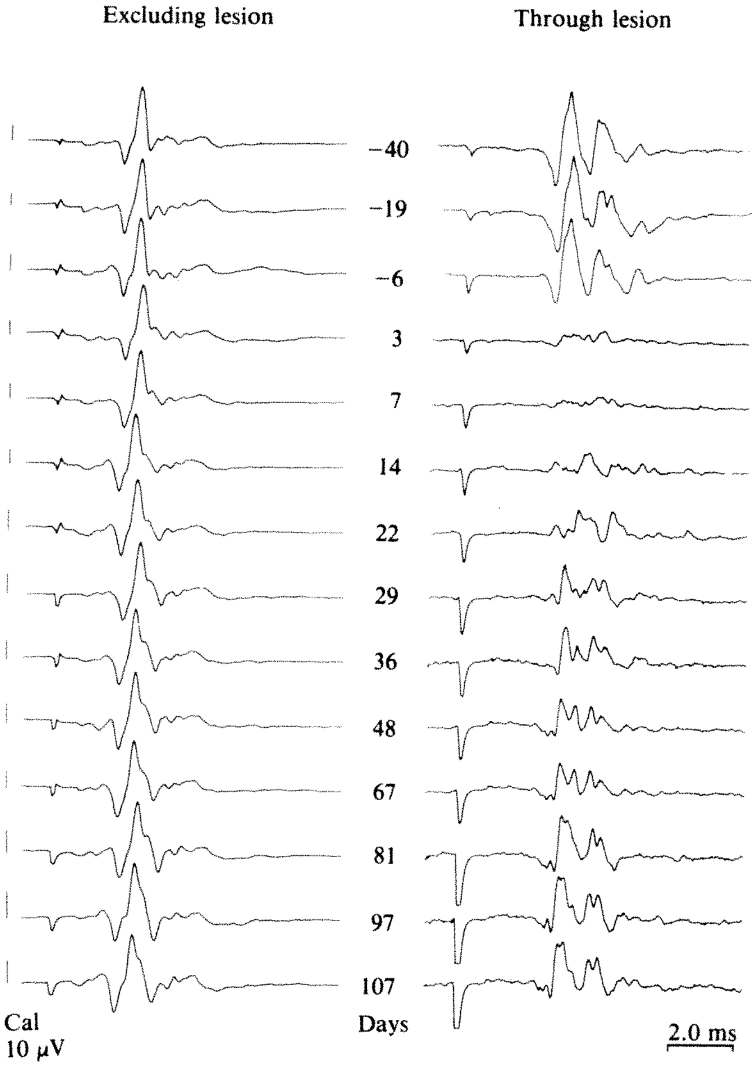


FIG. 5. Compound action potentials recorded from the saphenous nerves at different times during the development of a focal demyelinating and remyelinating lesion in the dorsal columns. To compensate for variables at the recording site the gain on each control response has been adjusted so that their peak-to-peak amplitudes are equal. The corresponding rostrally-evoked response has been adjusted by the same factor; each was recorded at 3.3 times the gain of its control. (Negativity at the active electrode in this and subsequent illustrations is recorded as an upward deflection.)

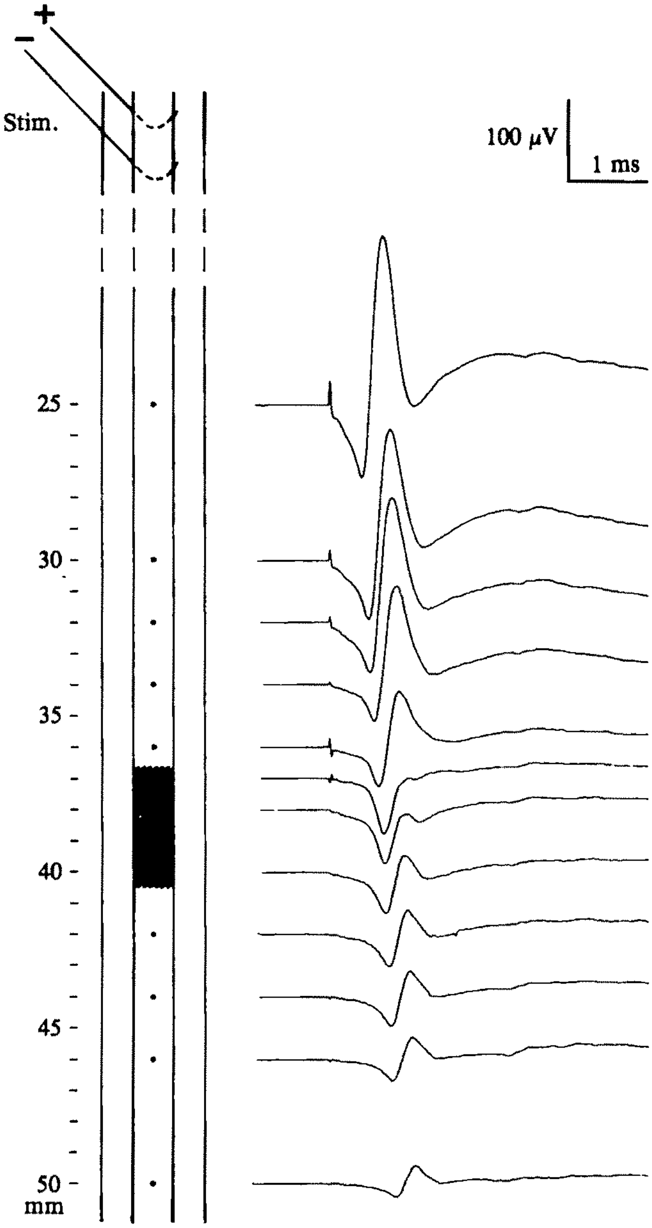


FIG. 6. Antidromic recordings taken from the dorsal columns seven days after the focal injection of LPC. The extent and location of the lesion (*shaded*) was determined by direct observation and later histological examination. At the proximal edge of the lesion the compound action potential is dominated by a positive wave indicating local conduction block.

The compound action potential at fourteen days (fig. 5) was greater in amplitude than those recorded at three and seven days and similar successive increments were observed at twenty-two and twenty-nine days. Subsequent changes in the compound action potential were less dramatic and the response showed no significant change after eighty-one days. The responses recorded at 81, 97 and 107 days were reduced in amplitude but otherwise similar to those made prior to the LPC injection. The compound action potentials obtained excluding the lesion (fig. 5) showed none of the changes just described although they were recorded at the same sessions and under the same conditions.

The latencies of the responses both through and excluding the lesion at the different recording sessions showed only a small latency variation which was attributable to small changes in temperature, that is, under the conditions of these experiments there were no significant latency changes in the long-term remyelinated fibres.

A measure of the security of conduction was obtained by determining the RPTs of the fibres contributing to the compound action potentials, using pairs of stimuli with various separations (*see* fig. 7). The three-dimensional array of responses recorded prior to LPC injection shows that normally the great majority of the fibres at each stimulating site have RPTs of 0.6 to 0.8 ms. The RPTs of the small number of fibres conducting three days after injection were possibly a little increased but were still within the control range. At fourteen days, however, the time when the reduced compound action potential started to increase in amplitude, it is clear that the majority of the fibres had prolonged RPTs of at least 1.6 ms and that some fibres had RPTs as long as 3 to 4 ms. At later recording sessions the RPTs progressively shortened so that the RPT distribution returned to normal at the time the form of the compound action potential had stabilized (fig. 7). The RPTs excluding the lesion remained constant.

Fig. 8 summarizes the relationship between the sequence of the physiological and the histological events. At three and seven days the recordings are reduced in amplitude; at these times demyelination is widespread. The increased amplitude observed at fourteen days corresponds with the onset of remyelination. Response amplitude and remyelination subsequently increase in step until two to three months after injection when both stabilize. The security of conduction (as measured by the RPT) improves during the period of myelin thickening.

The Importance of the Location of the Lesion

All the responses illustrated in fig. 9A were initiated from the rostral stimulating site in cat SC63 and they show the importance of the location of the lesion upon the recordings obtained. In this preparation the compound action potentials recorded from the right saphenous nerve show a similar progression to that examined in cat SC79 but the records from the left nerve do not. These latter records show only a small reduction in amplitude at three days and there is no significant subsequent increase in amplitude. The map constructed from the histological sections of this

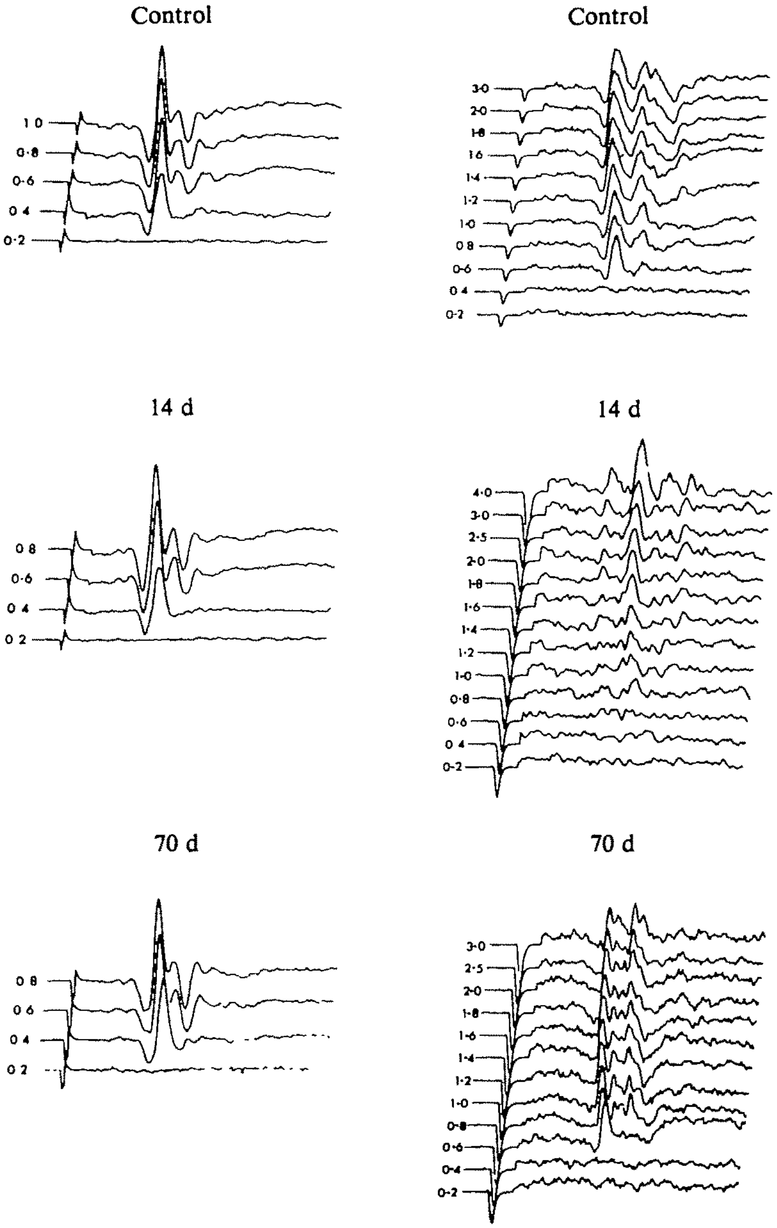


FIG. 7. Three-dimensional arrays of records obtained in response to the second stimulus of pairs in which the interstimulus interval is progressively increased. (Intervals are noted in ms at the beginning of the traces). The arrays were obtained at various times during the progression of the lesion; 'control' denotes recordings made before the injection of LPC. *Right*: Records evoked from the rostral stimulating electrodes, i.e. including the lesion in the conduction pathway. *Left*: Records evoked from the caudal stimulating electrodes, i.e. excluding the lesion.

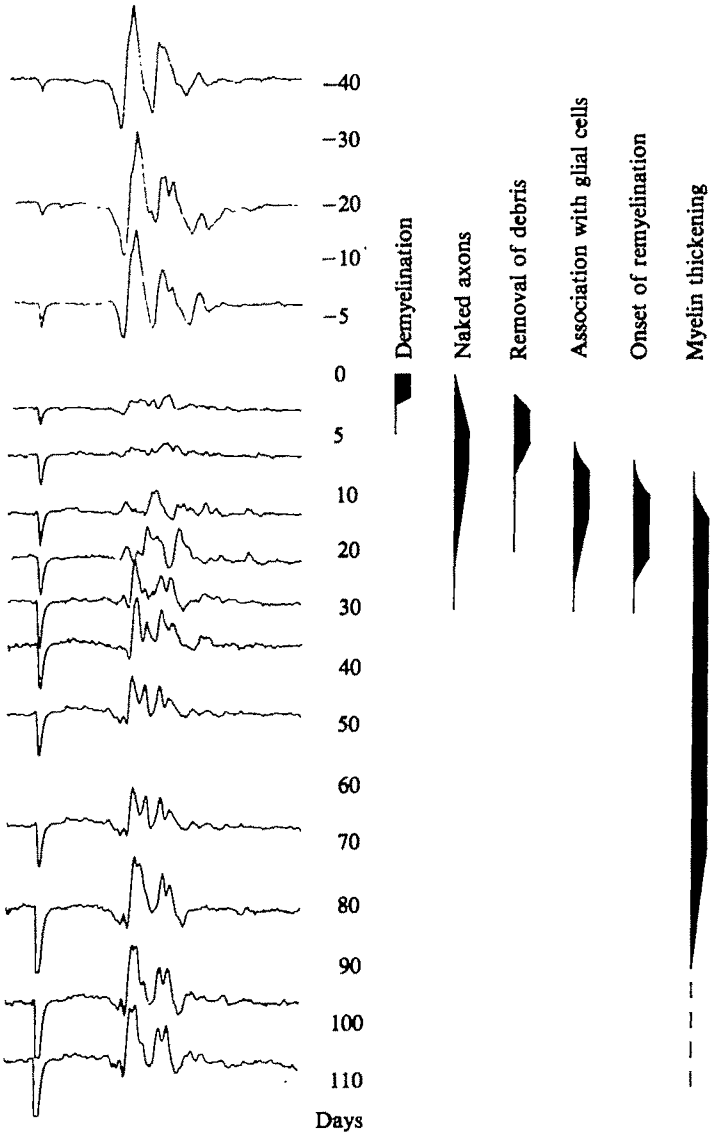
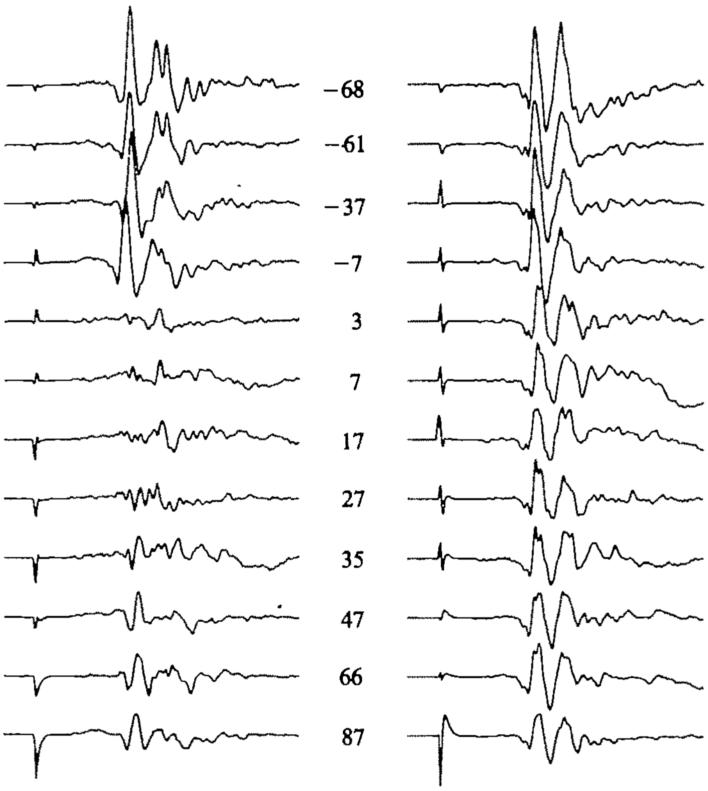


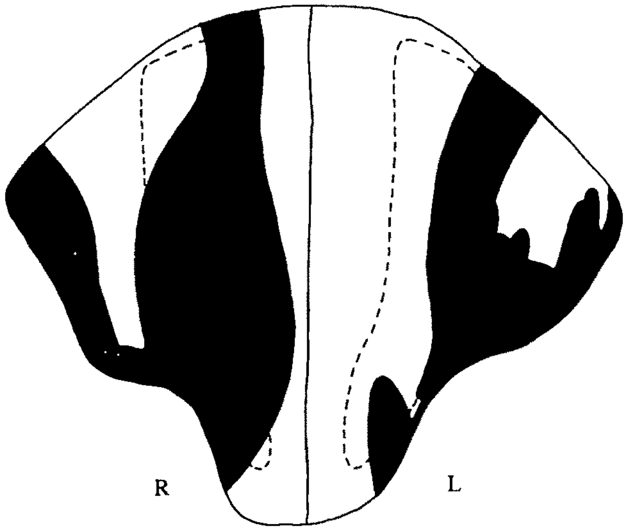
FIG. 8. Diagram showing the temporal relationship between the compound action potentials recorded through the lesion and the sequence of histological events at the lesion. The block and subsequent restoration of conduction correlate with the periods of demyelination and remyelination, respectively.

FIG. 9 (*opposite*). A, plot of the responses obtained from the saphenous nerves of cat SC63 at different times during the progression of the lesion. The responses illustrated on the left are from the right nerve and show the same sequence of changes as the records obtained from cat SC79. The responses to the right are also recorded through the lesion but are from the left nerve. Apart from a reduction in the amplitude at the time of injection there are no significant changes in the records with time.

FIG. 9. B, map of the dorsal columns of cat SC63 showing the extent and location of the lesion. The map was prepared by histological examination of the dorsal columns in representative transverse sections. The site of the fibres projecting to the saphenous nerves is also shown (*dashed outline*; from physiological studies in control cats). It is clear that only the right lesion involved most of the fibres from which recordings were made. The affected fibres present in the right dorsal column were remyelinated but there was also evidence that other fibres had degenerated. In the left dorsal column the several injections had repeatedly involved the same fibres and many of them had undergone Wallerian degeneration. Consequently few fibres were remyelinated on the left side.



A



B

animal is shown in fig. 9B. The approximate position of the saphenous fibres in the dorsal column is also indicated. It is clear that although the lesion in each dorsal column was large, only the lesion in the right dorsal column involved the majority of the fibres from the saphenous nerve. On both sides (especially the left) a proportion of the fibres underwent Wallerian degeneration and the persisting deficit in the number of fibres conducting is attributable to this loss.

Fig. 10 shows the location of the lesion in the dorsal columns of cat SC79 (recordings illustrated in fig. 5) and the location of the fibres to the saphenous nerves has also been determined (*see* Methods). It is clear that it was only the lesion in the right dorsal column that involved an appreciable number of the fibres from which recordings were made. The recordings illustrated in fig. 8 are from the right saphenous nerve of this cat. As with cat SC63, the recordings from the left nerve were largely unaffected by the lesion.

DISCUSSION

The outstanding finding of the present experiments is that secure conduction can be restored to central nerve fibres previously blocked by demyelination. The methods used have permitted the conduction properties of the same central nerve fibres to be examined serially during demyelination and remyelination. The amplitude of the compound action potentials was decreased during the period of demyelination and subsequently increased as remyelination progressed.

A correct understanding of the cause of the amplitude reduction in recordings obtained through the lesion during the first week is central to the interpretation of the subsequent recordings. A reduction in amplitude could arise from any of three effects: (1) simple dispersion of the impulses, (2) degeneration of fibres, or (3) conduction block in fibres with intact axons. The absence of fibres with prolonged latencies establishes that the first effect, dispersion, is not a significant cause. Some fibres do undergo Wallerian-type degeneration at the time of injection and so part of the amplitude reduction will result from the simple loss of fibres. However, the later increase in the amplitude of the recordings in the absence of regeneration demonstrates that fibre loss is not the only or even the major cause of the amplitude

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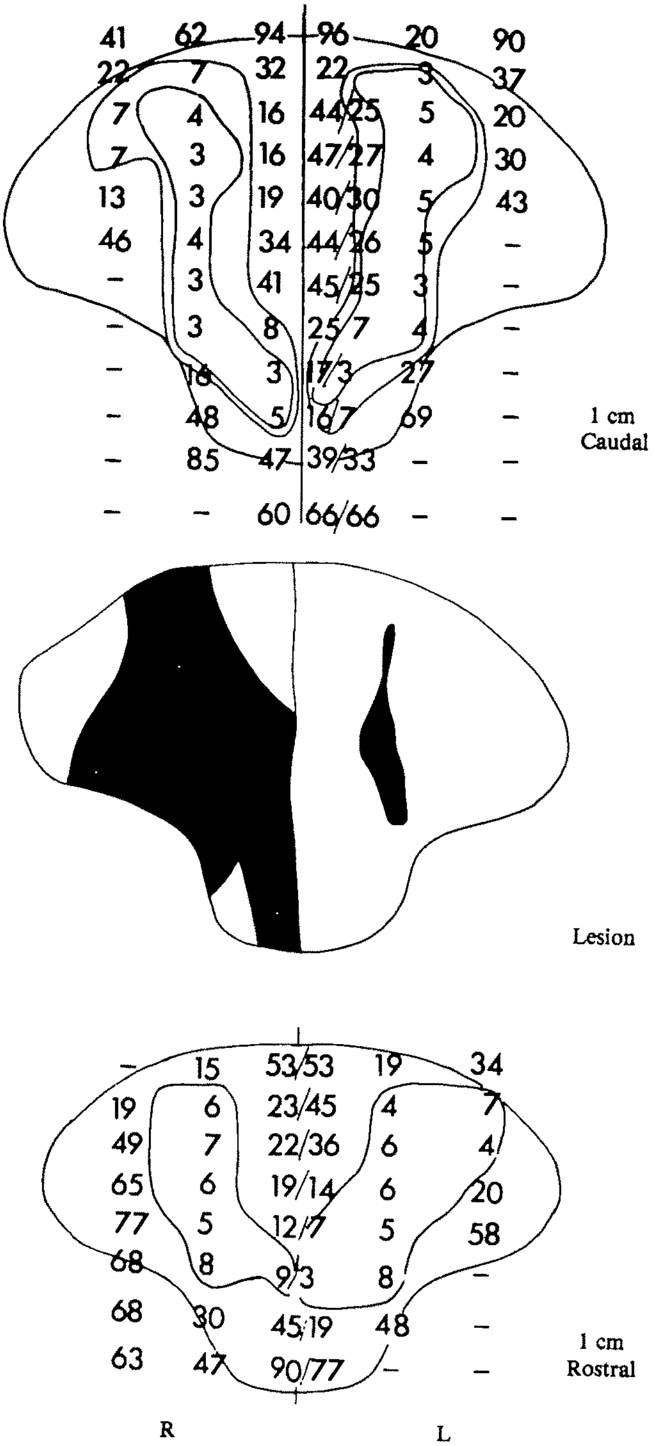
FIG. 10 (*opposite*). Map of transverse sections of the dorsal columns of SC79. The top and bottom map show the stimulus thresholds necessary to excite fibres in the saphenous nerves. Low thresholds imply the close proximity of such fibres and contour lines have been plotted around the low thresholds. Thresholds written as pairs (e.g. 44/25) denote the thresholds for fibres in the right and left nerves, respectively: otherwise the thresholds refer to fibres in the same nerves as the side in which the determination was made. The outline of the dorsal columns and the location of the midlines were estimated primarily from the physiological data but some reference has been made to histological sections. Dashes show the locations from which no saphenous fibres could be excited. The middle map shows the extent and location of the lesion and has been prepared by superimposition of drawings made from projected images of sections through the lesion. Nearly all the fibres projecting to the right saphenous nerve are affected by the lesion but few are affected on the left. For convenience, alternate tracks have been omitted.


41 62 94 96 20 90
22 7 32 22 3 37
7 4 16 44/25 5 20
7 3 16 47/27 4 30
13 3 19 40/30 5 43
46 4 34 44/26 5 –
– 3 41 45/25 3 –
– 3 8 25/7 4 –
– 18 3 17/3 27 –
– 48 5 16/7 69 –
– 85 47 39/33 – –
– – 60 66/66 – –
1 cm
Caudal
Lesion
– 15 53/53 19 34
19 6 23/45 4 7
49 7 22/36 6 4
65 6 19/14 6 20
77 5 12/7 5 58
68 8 9/3 8 –
68 30 45/19 48 –
63 47 90/77 – –
1 cm
Rostral
R
L

reduction. Conduction block must occur in many fibres. This conclusion is confirmed by the observation of a large positivity in the antidromic recordings made acutely at the lesion site after seven days. The small number of fibres still conducting through the lesion during the first week after injection were presumably unaffected by the LPC since their latencies and RPTs remained short. This interpretation accords with the histological observation that some fibres within the lesion remained intact.

Thus, during the first week, conduction is either blocked or unaffected. Over the same period the fibres in which axonal continuity is maintained are either demyelinated or normal and it is reasonable to conclude that the conduction block occurred in the demyelinated fibres and was a consequence of the demyelination. The completeness of the block during the phase of demyelination in the LPC lesion contrasts with the persistence of abnormal conduction in certain fibres in the central diphtheria toxin lesion (McDonald and Sears, 1970). This difference may be accounted for by the fact that diphtheria toxin causes both paranodal and segmental demyelination (Harrison, McDonald and Ochoa, 1972; Harrison, McDonald, Ochoa and Ohlrich, 1972; Ohlrich and McDonald, 1974) whereas LPC produces mainly the latter (W. F. Blakemore and K. J. Smith, unpublished observations). Computer simulations suggest that conduction can persist in paranodally demyelinated fibres provided the internodal capacitance and conductance do not become too great (Koles and Rasminsky, 1972), and Bostock and Sears (1978) have demonstrated prolonged internodal conduction times in experimental diphtheritic radiculopathy. In segmentally demyelinated fibres, however, the high internodal capacitance and conductance would prevent normal saltatory conduction (Koles and Rasminsky, 1972; Waxman, 1977) and fibres conducting in a similar manner to those found in the central diphtheria toxin lesion would thus not be expected to occur in the LPC lesion.

Since there is no significant regeneration in the central LPC lesion the increasing amplitude of the records during the second and third weeks must arise either from an increase in the number of fibres conducting or from a sudden and persistent synchrony of the fibres already conducting. The latter unlikely possibility may be discounted since the fibres concerned had a prolonged RPT and were therefore fibres which has not been conducting at seven days. Thus there were more fibres conducting during the second week than the first and the conclusion must be drawn that impulses which were previously blocked at the lesion now propagated through it. At this time the fibres are becoming associated with the remyelinating cells and thin myelin sheaths are seen on some fibres. It is reasonable to conclude that it is the remyelinating fibres to which conduction has been restored, and that the fibres which conduct do so in a saltatory manner. The further increments in amplitude during the next six weeks occur in step with the continuing remyelination of affected fibres.

Recent experiments have provided evidence that at least in some fibres in the peripheral nervous system, conduction across a demyelinated segment can occur in the absence of remyelination. In some types of lesion the normal process of saltatory conduction is converted to continuous conduction (Bostock and Sears, 1976, 1978; Rasminsky and Kearney, 1976) but in the peripheral LPC lesion there is evidence for the existence of saltatory conduction and 'physiological (Ø) nodes' in the demyelinated segment (Bostock, Hall and Smith, 1980). These observations raise the question whether conduction can occur in the absence of remyelination in the central nervous system. There has been no direct investigation of this possibility but the present indirect evidence suggests that it did not occur in the conditions of these experiments. The low velocity of conduction across the demyelinated segment (1-2 ms^{-1}) would result in delays of several ms over only a few internodal segments. In the present study averaging of many responses using a long sweep duration failed to reveal an abnormal number of units with long latencies. Although this result argues against the presence of either continuous or saltatory conduction in the absence of central remyelination it is not conclusive, since the latency of fibres with a region of such abnormal conduction might not be constant enough to permit averaging. Furthermore, the addition of the triphasic shapes of the action potentials could result in their cancellation. The possibility of conduction in the absence of remyelination under other circumstances remains: it might occur in very small central fibres, or if the temperature were lowered, or if the onset of remyelination were delayed. The presence or absence of conduction in demyelinated fibres before the onset of remyelination does not, however, materially affect the conclusions from the present experiments that conduction returns as remyelination commences and that it becomes secure while the new internodes are still abnormally thin and short.

Recent observations have provided evidence that gallamine triethiodide has a direct action on nerve (Schauf and Smith, 1981) and it is consequently important to consider whether the use of this substance as a relaxant could have affected our results. Gallamine in paralysing doses can reduce spontaneous firing in demyelinated central nerve fibres (K. J. Smith and W. I. McDonald, unpublished observations), which raises the possibility that part of the reduction in amplitude of the compound action potential was not due to conduction block but to the inability of spontaneously active fibres to transmit time-locked electrically evoked impulses. A significant contribution to apparent conduction block by this mechanism was excluded by the observation that the administration of gallamine did not change the compound nerve action potential.

There is evidence that the local application of gallamine can restore conduction block in peripheral nerve fibres blocked by demyelination (C. L. Schauf and K. J. Smith, unpublished observations) in virtue of its capacity to block potassium conductance (Schauf and Smith, 1981). If central nerve fibres behave like peripheral fibres in this respect, and the observed restoration of conduction was due to the effects of gallamine, it would be expected that as the potassium conductance diminished during remyelination gallamine would have less effect, and conduction block would reappear. The opposite was observed, that is, that conduction block became progressively less with time (fig. 5).

We conclude that the use of gallamine as a relaxant in our experiments did not influence significantly our results.

The long RPT of the newly conducting fibres is to be expected from the local circuit theory of conduction (Hodgkin, 1937*a*, *b*). When the myelin sheath is thin, much of the current generated by the active nodes is lost in overcoming the raised capacitance and conductance of the internode. As a result, the safety factor (Tasaki, 1953) is low and the RPT long. The gradual reduction of the RPT between two and twelve weeks coincides with the thickening of the remyelinated internodes and the consequent decrease in the capacitance and conductance of the myelin. The eventual return of the RPT to normal values is perhaps surprising at first in view of the fact that the remyelinated internodes remain noticeably thinner than normal. However, the new internodes are often also appreciably shorter than normal and consequently their capacitance and conductance may be, in general, lower than for a normal internode. Thus the safety factor across remyelinated internodes could be even higher than normal.

The failure of the recordings obtained through the lesion to attain their control amplitude even after three months is consistent with the small loss of fibres by degeneration as a direct result of the injection. However, despite the changes in amplitude, there is a striking similarity in the form of the records obtained through the lesion before and three months after the injection and this finding suggests that the central remyelinated fibres have a conduction velocity of near-normal values. The failure to detect the slowing of conduction which would have accompanied the prolonged RPT during the early phases of remyelination can be accounted for by the shortness of the lesion (approximately 3 mm) along any individual fibre relative to the total length of the conduction pathway (approximately 200 mm).

Although the injection of LPC always resulted in a lesion, there was not always an accompanying change in the action potentials initiated at the rostral stimulating site. For example, fig. 9A illustrates a preparation in which a clear sequence of changes was observed on one side only, despite bilateral injections and the production of lesions in each dorsal column. The explanation for this result is revealed by superimposition of the maps showing the distribution of the saphenous fibres and the extent of the lesion (fig. 9B). It is clear that the lesions in the left dorsal column, although large, are not affecting many of the fibres from which recordings were made. Other preparations in which no physiological changes were observed in one of the saphenous nerves provided useful controls for the effects of the direct trauma caused by the injection procedure.

The absence of a clinical deficit, even during conduction block, is to be expected since the lesions were small and confined to the dorsal columns. This finding is in keeping with recent experimental evidence relating to dorsal column function (*see* Wall, 1970; Myers, Hostetter, Bourassa and Swett, 1974).

Relevance to Human Disease

There is now convincing evidence that remyelination can occur in the human central nervous system (Prineas and Connell, 1979). It is therefore likely that restoration of conduction by remyelination contributes to clinical recovery. The magnitude of this contribution will be influenced by the number of fibres remyelinated. In multiple sclerosis, remyelination appears to be limited to a comparatively small number of fibres at the edges of the plaques (Prineas and Connell, 1979). Restoration of conduction by remyelination is thus likely to play only a small part, if any, in the characteristic remissions of multiple sclerosis. It is likely to play a much larger part in recovery from acute and chronic compressive lesions of the central nervous system.

Experimentally, acute compression of the spinal cord is accompanied by demyelination which is followed by remyelination, the new myelin sheaths being structurally similar to those observed in the LPC lesion (Gledhill *et al.*, 1973; Harrison and McDonald, 1977; Gledhill and McDonald, 1977). It is interesting that the time course of recovery of sensation over several weeks following flexion/extension injuries of the cervical cord in man is similar to that of the recovery in conduction which we have observed.

Clifford-Jones *et al.* (1980) investigating experimental orbital tumour, have shown that remyelination commences while the optic nerve is still compressed. It is likely that the compression holds conduction in the remyelinated fibres in abeyance by direct pressure block. If this is so, recovery of conduction in remyelinated optic nerve fibres could account for the rapid improvement in vision seen directly after removal of tumours compressing the anterior visual pathways (Kayan and Earl, 1975). The progressive improvement in security of conduction which parallels the increasing thickness of the new myelin sheaths would also contribute to the slower phase of visual recovery seen in the succeeding months (Cushing and Walker, 1915; Symon and Jakubowski, 1979). It must be stressed, however, that other mechanisms may contribute to recovery of visual function, the time course of which is similar to that observed with large destructive lesions of the anterior visual pathways characterized by Wallerian-type degeneration and persistent demyelination with little or no remyelination. The nature of these mechanisms is still poorly understood and has been discussed elsewhere (Jacobson, Eames and McDonald, 1979; Bostock and McDonald, 1981).

SUMMARY

Conduction has been examined serially through the experimental demyelinating lesion produced by the direct micro-injection of lysophatidyl choline into the cat spinal cord. Conduction was blocked during the phase of demyelination. Remyelination commenced during the latter part of the second week, and conduction through the lesion was restored in some fibres at this time. The refractory period of

transmission was initially prolonged. As remyelination proceeded, conduction was restored in increasing numbers of fibres. Within three months the responses were stable and the refractory periods of transmission had returned to normal even though the new internodes were still abnormally thin and were generally shorter than normal. Restoration of conduction by remyelination is likely to contribute to recovery from compressive and traumatic lesions of the central nervous system but probably plays little part in the remissions of multiple sclerosis.

ACKNOWLEDGEMENTS

The expert technical assistance of Ms A. Brandon and Mr R. Patterson is gratefully acknowledged. The work formed part of a Ph.D. thesis (K.J.S.) accepted by the University of London. The work was supported by the Medical Research Council.

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(*Received January 21, 1981*)

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NOTICES OF RECENT PUBLICATIONS

The Selected Papers of Gordon Holmes. Edited by C. G. Phillips. 1980. Pp. 488. Oxford University Press. Price £20.00.

Heroes there are in every discipline, and in neurology, none but Hughlings Jackson rivals Gordon Holmes. The senior neurologists alive today who clerked with him at Queen Square do not hide their worship. His friends, on his 80th birthday, published a *Festschrift*; it contained only his own papers. A second commemorative was planned for his 90th birthday, but he died before its completion. Now, in honour of his 100th anniversary, we have a second book: only his own work, and more complete than the last. Why this adulation?

The book gives the main reason, in showing again the kernels that have so richly borne fruit. There are the Croonian and Hughlings Jackson lectures on cerebellar symptoms in man; and those who have used them as inspiration and guide may be surprised that he did anything else. But visual scientists also will find their own fundamental icons, ranging from retinocortical mapping to visual perception and the psychic control of gaze. Students of eye movement will see papers on oculomotor control that even today stand as fair summaries of our knowledge on that subject. Experts on the urinary bladder and the neural control of micturition will find that modest paper that appears to have begun a discipline: a short article on bladder control after acute spinal cord injury, together with the methods of study, in companionship with the classic papers on the chronic effects.

Of his major works, only one is omitted. This is the paper (with Head) on somæsthesis, which sets down our current philosophy (Head), method of examination (Holmes), as well as the symptoms themselves after cortical lesions (Holmes and Head). It is simply too long (Head). The editor attempts to set it right by giving a later paper of Holmes, this time in his own spare words, that amends and corrects the earlier work. In all, the specialists of today may well be surprised to find the roots of so many mixed among their own in the work of this one man.

How did he do it? A private practitioner, he never had a research grant, laboratory, technician, or academic post. Much of his best work was published from military hospitals in Europe, working and writing nights, in the years 1914–1918. He designed and made his own tools, where none existed. He wrote with a simplicity and elegance not of his time; that alone can recommend him to writers of today.

Why did he do it? It is unfortunate that the book does not pull together the many stories told and written about him—his energy, enthusiasm, fierceness, gentleness, strength. But these will doubtless surface in memoirs, and become part of the next commemorative, which will then be complete.

This, then, is the documentation of one of our greatest heroes. It is necessary reading for the young, and for those not too old to learn, to wonder, and to admire.

W. T. THACH and W. M. LANDAU

The Brain. A Scientific American Book. 1979. Pp. 149. San Francisco and Oxford: W. H. Freeman. Price £8.30. (Paperback £3.90.)

There is no shortage of books on the brain. At best most of them are worthy but boring, and good ones are nearly as rare as hens' teeth. Ask almost any neurobiological undergraduate to name an inexpensive, lively, up-to-date, stimulating and readable book about the brain and (s)he will be hard pressed to get beyond Kuffler and Nicholls. The appearance in book form of the eleven articles on the brain which first appeared in a single issue of *Scientific American* is therefore welcome.

The first point to note is the list of contributors. A star-studded cast never guarantees a good play, but it certainly helps. Every contributor to *The Brain* is a notable scientist whose productivity far exceeds that merely measured by number of published papers. They are people with ideas and they have been encouraged to air them. It is probably best to read the opening and closing chapters first, if only because they will tell you whether you would be wasting your time with those in between. The first, by Hubel, is an unusually trenchant account of what brain scientists are trying to do. Some questions are dismissed as not worth asking, for example 'Can the brain understand the brain?', or 'Is the brain a computer?'. Others are identified as premature because we still lack the means to tackle them, for instance the cellular basis of human learning and memory, or as 'fads that sometimes amount to a derailment of thought', such as the attempts to transfer memories by grinding up educated flatworms and feeding them to their unschooled companions. The 'right' questions are familiar enough—how do nerve cells work? How are they connected and do any general patterns emerge? How does the brain develop? What kinds of stimuli do neurons respond to selectively? And how is reception translated into bodily action? Not surprisingly the bulk of the book is devoted to questions like these. The last chapter, by Crick, is not unlike the first in that it considers and evaluates various general approaches to brain research. Introspection is shown to be a subtle deceiver, and philosophers get short shrift for failing to understand information processing. Artificial intelligence is given credit for revealing rather than solving problems. The black-box approach is mourned for leading to numerous equally plausible but incompatible theories that are usually shown to be too simplistic as soon as an attempt is made to test them. It is said that we cannot understand the brain by studying only its 10^{11} components, and that in any case the rate at which information is gained is low, compared with that available. Comments like this will delight or infuriate, and I think every one of them could be challenged, but one senses that Crick was invited to be provocative. And he is not completely negative. For example, the *combined* study of behaviour and the inside of the brain is singled out for praise. It is in considering future strategies that the chapter comes close to pessimism. A few methodological changes, such as recording from many neurons individually but simultaneously, are recommended but no attempt is made to conceal the fact that we sometimes use new methods to get new results in order to generate new ideas. It seems an odd way to proceed but what Crick finds conspicuously absent in brain research is any broad framework of ideas. It looks as if we need a lot more experiment driven by low-level hypotheses before any grand scheme can emerge.

Turning now to the centre of the sandwich the chapter by Stevens is about the neuron, or more precisely about membrane proteins and their role in the nerve impulse and transmitter release and uptake. If this sounds narrow, it is; and although the work described is elegant and important I suspect that the general reader will make little of some of the technical complexities such as the co-ordinated action of five types of specific ion-channel, why the thinness of the cell membrane allows a potential difference across it to generate a large electric field, and the inadequately labelled electron micrographs. Perhaps the topic was wrong, because I doubt that anyone else could have done a better job.

Moving from one cell to groups of cells Kandel makes a good case for studying simple nervous systems such as that of the snail Aplysia. While many will remain unconvinced that recovery from habituation resembles forgetting in higher animals, or that sensitization is a precursor of classical conditioning, it would be a mistake to judge the chapter on these grounds. Its strength lies in the clear demonstrations that (*a*) many neurons can be individually identified and that they and their connections are species-invariant, (*b*) a single transmitter can produce excitation or inhibition depending on the post-synaptic receptor, (*c*) a single neuron can form both excitatory and inhibitory synapses, (*d*) the site of short-term habituation is the depression of the calcium current in presynaptic terminals. It matters little that things may be different in vertebrates; the work on Aplysia shows what it is possible for neurons to achieve.

In describing the organization of the brain Nauta and Fiertag produce a gem. They describe some general principles, e.g. all thalamocortical connections are reciprocated and only 0.1 per cent of neurons are sensory or motor, but dwell almost apologetically on connections. Most neuroscientists know a lot about some part of the brain but few know much about all of it. Nauta is one and he and Fiertag use that to let us see the house as well as the bricks. This would be a good chapter for anyone bogged down by the minutiæ of neuroanatomy. Cowan's chapter on brain development is similarly 'global' and useful for the student. It is not afraid to dwell on some old problems, for example how nerve fibres know where to go, but introduces very recent evidence where relevant, e.g. barrel fields in mice. It is also full of examples of how the apparently bizarre or ridiculous can throw light on the everyday, for example rotating or transplanting eyes in frogs and grafting extra limb-buds in chicks.

It is a sign of the times that the chemistry of the brain requires an entire chapter. Iversen takes us through the evidence that there may be up to thirty different neurotransmitters and describes the biochemistry of chemical transmission. All this is sound stuff but the chapter is slightly marred by including too much that is controversial without frequent warnings to the incautious reader. Examples are schizophrenia and dopamine, enkephalins and acupuncture, vasopressin and memory.

The chapters by Hubel and Wiesel (Vision) and by Evarts (Movement) show what has been achieved by allying new and old techniques with good ideas. The work is so well-known that few readers will be unfamiliar with it, but it is useful to have a short account of the sustained piece of research by Hubel and Wiesel showing that the striate cortex, and probably the rest of the cortex, is composed of a large number of essentially identical building blocks and that in broad outline we know how the striate cortex works. While Hubel and Wiesel have many emulators, Evarts has ploughed a bit of a lonely furrow until recently. Strangely his chapter does not attempt to explain the relative neglect of the motor system (for example that it is difficult to specify and control and even identify the stimulus that provokes movement) or why we ignore it at our peril (for instance that we can never fully understand perception without studying responses). However it clearly demonstrates the value of doing electrophysiology with conscious behaving animals and convincingly shows that many problems will not be solved without doing so.

Finally there are the chapters by Geschwind and by Kety. Both are about brain disorders but the resemblance ends there. Geschwind shows how function and its localization can be illuminated by brain damage that produces language disorders, disconnection syndromes, agnosia and amnesia. Much of it is classical neurology and some of it is a bit too reminiscent of his earlier article in *Scientific American*. However, there are some exciting recent developments such as functional hemisphere differences in a variety of animals and the tantalizing possibility that normal expansion of a particular histologically distinct region of the language area in the right temporal lobe fails to occur in dyslexia. Kety's chapter concerns the ætiology and measurement of the physical disorders of the brain, on which it is simple and instructive, and the role of such disorders in psychological states, where it is more controversial. The putative role of chemical disorders in causing psychotic conditions rather than being a result of them or of attempts to treat them arouses disputes that are not even hinted at. Even so, Kety does show that chemical disorders *can* cause cerebral and mental disturbance and that the possibility of explaining and treating schizophrenia as one does physical illness is so important that it must be pursued.

How does the book appear as a whole? Although I suspect that few will read it from cover to cover and judge it as a single work there are some things one can say about all the contributions. First, they bear the stamp of *Scientific American*, that is they are simply and clearly written, the illustrations are excellent, we are often told things twice in a slightly different way by repeating text in figure legends, and homespun analogies abound, for example 'a one-neuron nervous system is like a doorbell'; 'cells are interrogated with a microelectrode'; 'the nerve impulse sweeps along the axon like a flame along the fuse of a firecracker'. Secondly, and unlike some other scientific publications, there is mercifully little overlap between chapters. Thirdly, each chapter ends with a statement about the most pressing unsolved problems. Finally the book abounds with words and phrases like 'baffling', 'mysterious', 'not yet fully understood', and 'still at an early state', all of which correctly reveal our massive ignorance.

Who will read the book? It is cheap enough to attract students and they will probably and rightly provide the market. But no chapter can be more than hors d'œuvre and further reading will be essential.

It is therefore disappointing that some of the bibliographies at the end of the book provide references that give detailed accounts of esoteric points (*e.g.* those provided by Crick) and that they do not all (like Cowan's) lead the reader to extended discussion of broader issues. Lastly, does the book mislead by omission? It is not difficult to think of topics that could have been included, for example hearing or emotion. My candidate would be the problems of studying behaviour. But on the whole the selected topics are a reasonable indication of what neurobiologists are doing, and why.

I usually agree with Dorothy Parker that 'I don't review books any more. It cuts in too much on my reading'. But not this time.

ALAN COWEY

The Endocrine Function of the Brain. Edited by Marcella Motta. 1980. Pp. 475. New York: Raven Press. Price $57.80.

It is difficult to guess from the title what problems are included in a survey of the brain's endocrine functions. Chemical transmission at any terminal may, by definition, become an endocrine event whenever terminals end without forming a synapse, as happens, for example, in 95 per cent of monoaminergic boutons. However, the book is concerned mainly with hormones in the usual sense, though it casts its net wide. The first two chapters deal with the traditional 'endocrine brain', median eminence and hypothalamus, but already point to the fact that the production of neurohormones is not restricted to hypothalamic structures. The next two articles deal with the brain as target tissue for hormones. This has recently been a field of great scientific activity, leading to the identification of steroid hormone target neurons and their receptors. The rapid change which hypothalamic and pituitary receptors can undergo forms the basis for the changes in responsiveness to hormones active during the oestrous cycle.

Steroid metabolism in brain tissue has important physiological effects, which are most conspicuous in brain development, facts dealt with in the next two chapters. Then follows the discussion of the difficult problem of localizing with precision releasing factors and other hypothalamic hormones, including α-MSH and ACTH. Chapter 9 is devoted to the enzymatic degradation of brain peptides and to the rather meagre evidence of their release. This is followed by the demonstration of peptide-containing nerve terminals in the ventricular spaces.

A paper by thirteen authors deals with interactions between releasing hormones, steroids and cyclic AMP as a basis for their effect on the anterior pituitary. The next chapter (one author only) covers the wide field of peptide receptors, has a long list of references and contains the interesting remark that there has only been one report of a successful demonstration of receptors for substance P. Interactions of œstrogens with hypothalamic dopaminergic neurons, and effects exerted by midbrain, hippocampus and amygdala on hypothalamic function form the next chapters. An article on the pineal gland shows how great the gaps are in our understanding of the role of this enigmatic organ. The book concludes with a chapter on recent views on the central angiotensin system, with another on the hormones of the posterior pituitary, with a survey of the clinical aspects of hypothalamic disease and with an evaluation of diagnostic tests in endocrine disorders.

It will be obvious from the review that this book contains much recent information which is of great interest to physiologists, endocrinologists and neurologists. The majority of articles have a clear objective which is well-defined in its title. An occasional chapter is ill-defined in its aims and would have been better integrated if subjected to some rigorous pruning.

The book is well produced, but in some of the photomicrographs the magnification is missing.

M. VOGT

Handbook of Pharmacology. Edited by L. L. Iversen, S. D. Iversen and S. H. Snyder. Volume 14. **Affective Disorders: Drug Actions in Animals and Man.** 1978. Pp. 379. New York and London: Plenum Press. No price stated.

This last volume of the series is clearly written with the clinician in mind. It deals comprehensively with the drugs used in depression and mania. The pharmacological basis is obtained from experiments on animals, often carried out after a chance observation on a depressed or manic patient who was given the drug for a purpose unconnected with the mental illness. The first five chapters are devoted to the inhibitors of monoamine oxidase and to the tricyclic antidepressants. Theories about the mode of action of these drugs in fighting depression could not have been more varied, each successive explanation trying in vain to accommodate all facts. The discovery of iprindole which could not be explained by any of the previous theories drew attention to the views of Sulser and colleagues who suspect that the crucial action has to be sought in late actions of the drugs, probably at the receptor sites. They point out that inhibition of MAO or of uptake are events which occur at the very first contact with the drug, whereas the clinical improvement takes weeks to develop, allowing ample time for adaptive responses of the tissue which may be crucial to the beneficial effect.

There is also a detailed discussion of the great variability of the metabolism of the tricyclic drugs in different species, and on different organs of the same species. Furthermore, demethylation of tertiary amines, one of the most important metabolic transformations, leads to products with a different profile of interaction with noradrenergic and serotonergic neurones. However, in spite of all these variables Chapter 5 manages to formulate recommendations to the clinician of treatments which have proved useful. There is some disagreement between authors about the classification of depression which theoretically should be treated differently.

The last three chapters deal with lithium. Its success in the treatment of mania is undisputed. So is its toxicity which requires continuous supervision of the patient, even if the psychosis is satisfactorily controlled. The partition of Li between plasma and red cells may have a prognostic value but may also forecast toxicity. The extension of Li therapy to the prophylaxis of bipolar depression is a newer development, and has led to the question of its value in unipolar depression. There appears to be good evidence that it can indeed be beneficial in recurrent depression. It is interesting that the prophylactic use of Li has created certain problems. Whereas Li does not interfere with normal intellectual activity or restrict the emotional range, some creative cyclothymic individuals who feel that they do their best work in their hypomanic phase may object to the stabilizing action of the therapy and rather risk a frank attack of mania or depression than continue the treatment. The book ends with a short review of the treatment of depressed patients with rubidium, the rationale being that it is an antagonist of Li. A few patients improved, but the series was too small to give more than preliminary results.

The book is easy to use for anybody searching for an answer to a particular question, and the whole volume will make interesting reading for doctors or scientists interested in the practical or theoretical aspects of therapy with drugs used in affective disorders.

M. VOGT

Genes and the Mind. Inheritance of Mental Illness. By Ming T. Tsuang and Randall Vandermey. 1980. Pp. 143. Oxford University Press. Price £5.95.

This book was written for the general reader, with the concerned patient or relative in mind: it is also directed to doctors and paramedical workers who are not specialists in the field of psychiatric genetics.

An outline of genetical mechanisms is followed by a section on the principles and practice of genetical counselling. Schizophrenia, affective disorder, dementia and alcoholism have been selected for a full review of the evidence for genetical factors in ætiology, and inferences from published papers are critically assessed.

The book is accurate and will be a valuable guide to the readers to whom it is directed.

R. T. C. PRATT

Mindsplit. The Psychology of Multiple Personality and the Dissociated Self. By Peter McKellar. 1979. Pp. 188. London: J. M. Dent. Price £7.95.

The concept of disconnection has been a stimulating principle in neuropsychology since its revival by Geschwind in his two valuable papers in this journal in 1967. The concept of dissociation has also a very long history in psychiatry, attracting close attention in the school of Janet in the early years of this century, and is due for revival in the field of psychology and psychiatry. Various aspects of dissociation are considered—sleep, dreams, hypnosis, double personality, multiple personality, automatisms and hysteria. An especially interesting chapter is that on imagination and visual imagery, as exemplified in particular by the self-description of Enid Blyton and her method of composition.

In spite of its eye-catching (though appropriate) title this is a scholarly book written in a lively manner. Valuable general conclusions are drawn from the many examples of dissociation that are quoted. This is an important book for psychiatrists, and can be read with enjoyment by neurologists. I recommend it whole-heartedly.

R. T. C. PRATT

Stereotaxis in Parkinson Syndrome. By R. Hassler, F. Mundiger and T. Reichert. 1979. Pp. 315. Berlin, Heidelberg, New York: Springer-Verlag. Price DM 280.00.

This book is based on the stereotactic work of the neurosurgical centre at Freiburg from 1950 to 1977, and its largest section is the report by Hassler of the post-mortem findings in 17 cases (involving 23 operations) with special reference to the accuracy of the surgical procedures. When the target was believed to have been reached the area was stimulated electrically before making the lesion, and the declared aims of the book are, (1) to relate post-mortem findings to the corresponding particular effects of stimulation and of functional loss, as well as to the clinical result, and hence, (2) to deduce the function of certain cerebral systems, and (3) to decide on the best therapeutic steps and their targets. Obviously it is Hassler's book, based on the work and statistics of his surgical colleagues. The clinic mortality is given as 0.83 per cent and 7 of the 17 patients reported here died from pulmonary embolism and not from the direct effects of the operation.

As at other centres the usual target was the nucleus ventro-lateralis anterior (oralis) of the thalamus, but the best results for tremor by itself were obtained from coagulation of the nucleus ventro-lateralis posterior or even the dentato-thalamic fibres posterior to it.

The pathological sector is preceded by a detailed description of the basal gangliar system, including an unusually full account of the substantia nigra and what is known of its physiology, and is followed by a long section on correlations: of the accuracy of reaching the target, of the reliability of the radiological points of reference, of the effects of stimulation before making the lesion, of the clinical results and of unusual symptoms before or after the operation. The parkinsonian tremor is attributed to synchronization of the normal fine postural tremor and it is suggested that the prevention of such synchrony is a function of the substantia nigra. Finally, there is an atlas of twelve sections of the basal ganglia and thalamus with key diagrams showing the positions of the relevant thalamic nuclei.

The book is very costly but it seems to have been produced regardless of expense; it is lavishly illustrated and printed throughout on fine art paper. The English of the main text is almost perfect but in the long captions of the illustrations the omission of the definite article spoils the style. Misprints are rare but at one point there is an unfortunate lack of a decimal point in the dimensions of the thalamus.

There is a good bibliography and it contains references to eighty contributions by Hassler during the years 1937 to 1977 and many papers by his co-authors.

J. PURDON MARTIN

Handbook of Clinical Neurology. Volume 39. **Neurological Manifestations of Systemic Diseases.** Part II. Edited by P. J. Vinken and G. W. Bruyn. Amsterdam: North-Holland Publishing Co. Price Dfl. 245.00.

This volume begins with seven chapters on further neurological aspects of malignant disease and paraproteinæmias, followed by ten dealing with various vascular disorders. The whole is completed by pieces on diverse topics, including the adrenal gland, the neurology of gastro-intestinal disease and eclampsia.

Young and Posner have contributed an excellent chapter on the toxic effects of chemotherapeutic agents on the nervous system. Apart from a comprehensive account of the clinical aspect of their subject, they have provided a useful summary of therapeutic indications for various drugs, together with observations on their modes of action. Cairncross and Posner write authoritatively on the neurological complications of malignant lymphomas, as does Osuntokun on Burkitt's lymphoma. Abramsky reduces the sometimes bewildering clinical story of the macroglobulinaemias to welcome coherence. Among the contributions on vascular disorders, those of Cochrane and LeBlanc, on lesions of the aorta and their neurological complications, and Lambert and Fairfax, on cerebral effects of cardiac dysrhythmias, read well. The relationship of the adrenal gland was entrusted to Van Der Sande and Van Seters; their forty page contribution provides a welcome source of information.

Now that this remarkable venture is nearing its conclusion the editorial design remains unaltered and clear. *The Handbook* is unique in its encyclopædic scope. Volume 39 will be particularly valuable to neurologists working in general hospitals and therefore continually exposed to problems deriving from the neurological effects of systemic diseases.

R. A. HENSON

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Brain

A Journal of Neurology

Volume 104 Part III September 1981

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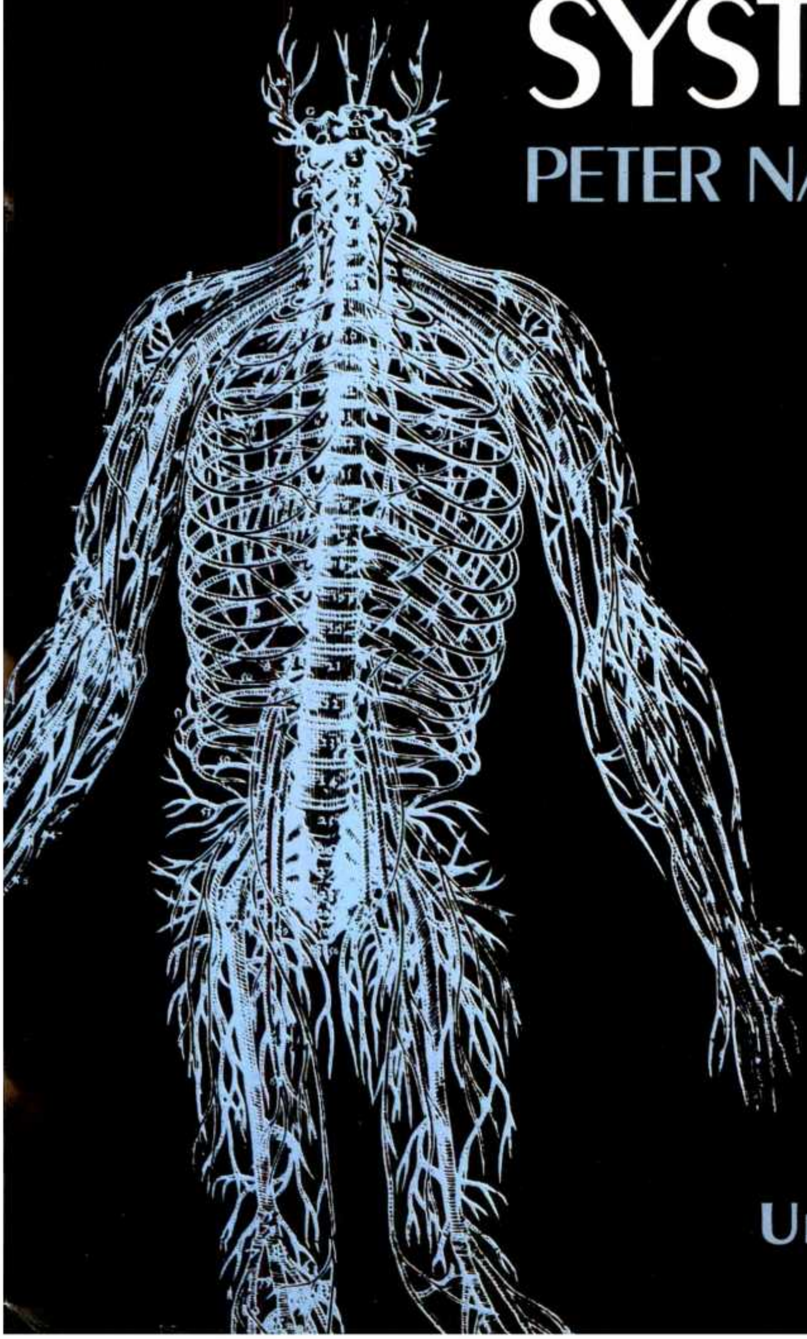

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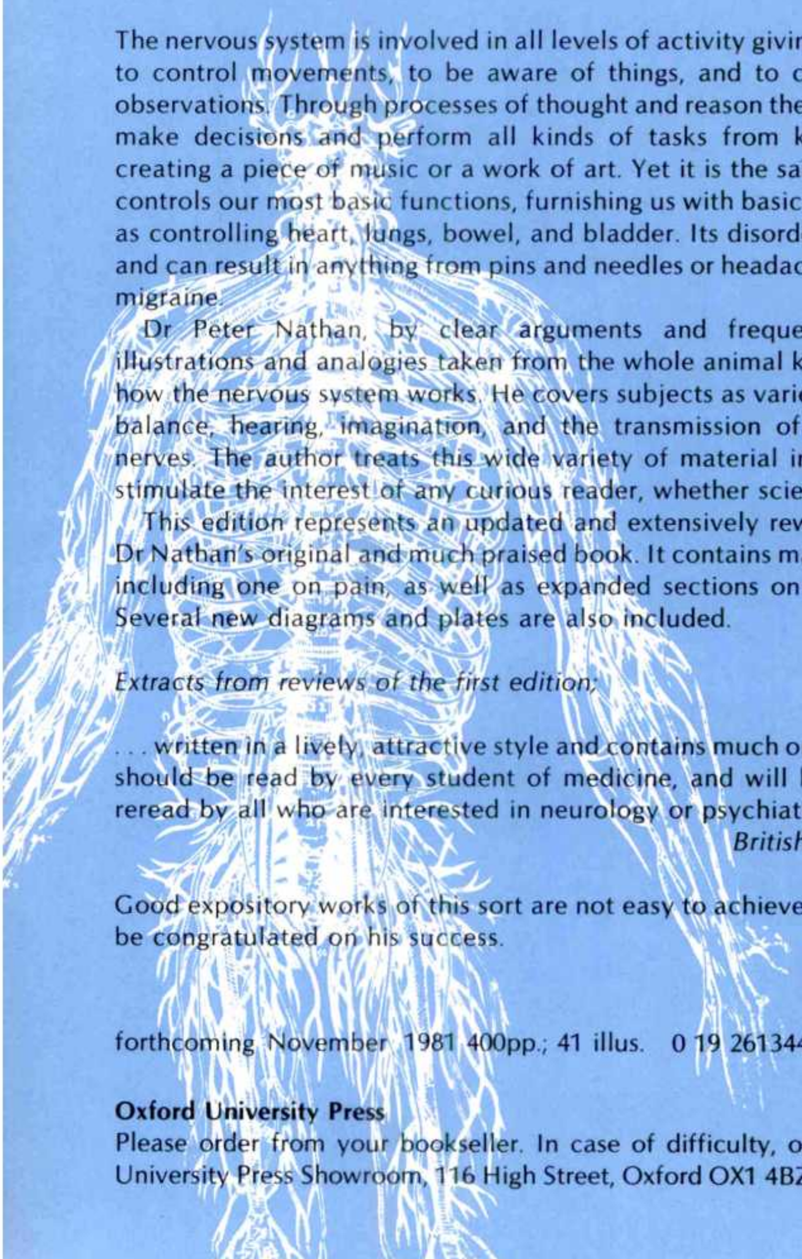

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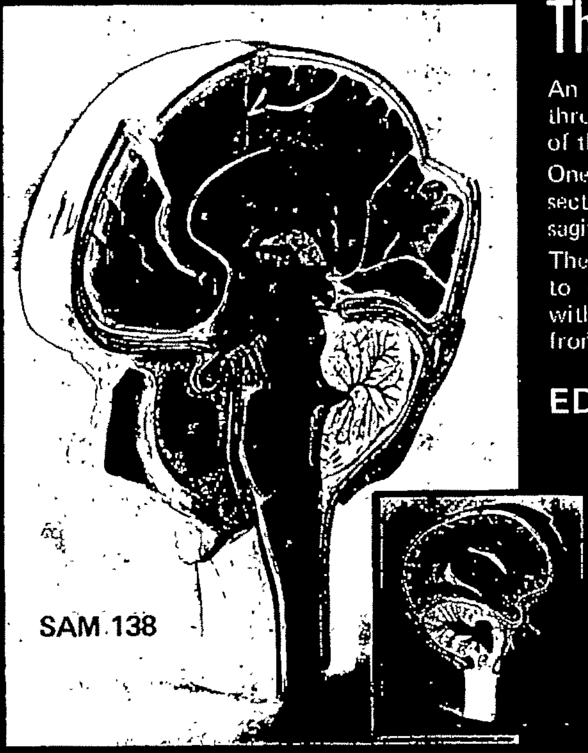

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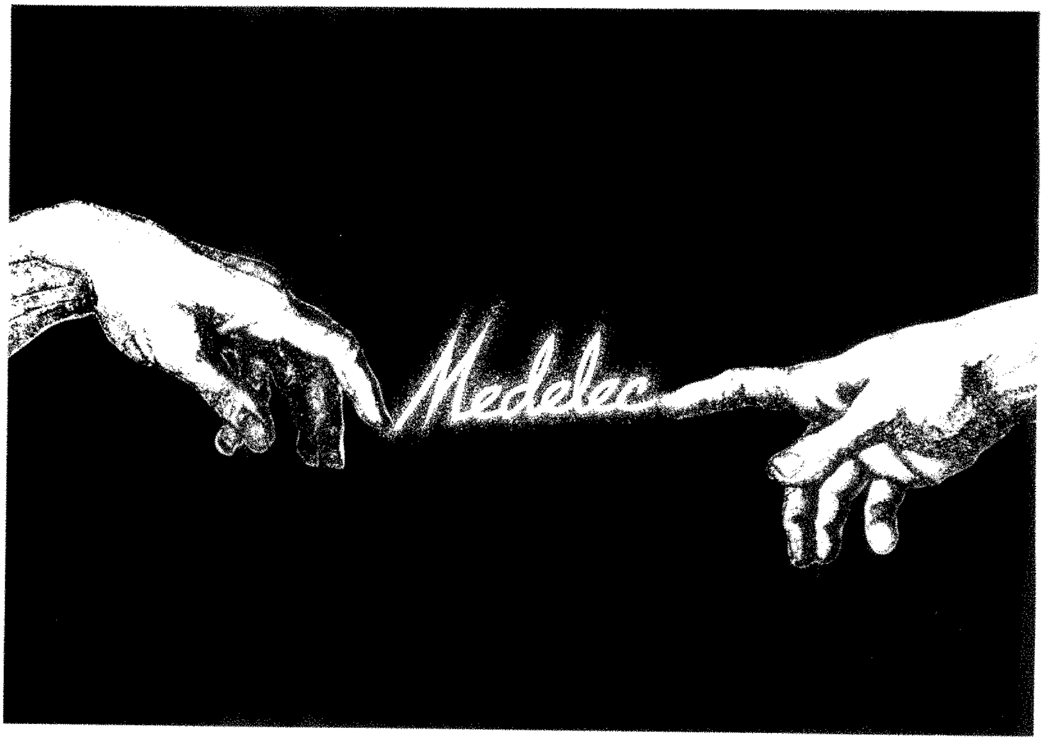

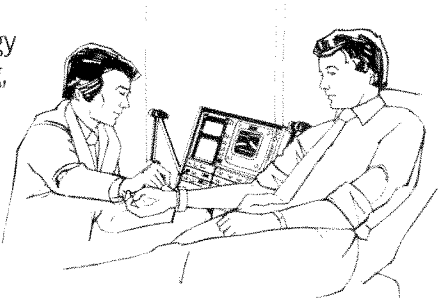

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PHONOLOGICAL AGRAPHIA AND THE LEXICAL ROUTE IN WRITING

by TIM SHALLICE[1]

(*From the Psychology Department, National Hospital, Queen Square, London WC1*)

INTRODUCTION

THERE has been much research in recent years on neurological disorders of written word processing. This work, however, has concentrated very heavily on the reading process to the relative neglect of the writing process. A small number of group studies of writing deficits have been undertaken, both of specific agraphias (Dubois, Hécaen and Marcie, 1969; Basso, Taborelli and Vignolo, 1978) and of the agraphias in relation to other disorders, for example, the aphasias (Kinsbourne and Warrington, 1964; Dubois, 1977; Weigl and Fradis, 1977; Wapner and Gardner, 1979). Recent information-processing analyses of the writing process in normal subjects, however, suggest that many sub-systems are involved (*see* Ellis, 1980; Morton, 1980). If, as seems probable, most of these sub-systems are situated in the left hemisphere, group studies of neurological patients may not be a sufficiently subtle methodology to greatly illuminate the functional architecture of the writing process (*see* Shallice, 1979). However, the upsurge of interest in the acquired dyslexias has arisen through the use of single case studies combined with the adoption of an information-processing approach. This combination of methods has led both to the isolation of new syndromes and to a much greater degree of integration between studies of acquired dyslexic reading and of reading by normal subjects (*see*, for example, Coltheart, Patterson and Marshall, 1980).

By contrast with reading, there have been very few studies of agraphic patients in which detailed quantitative analyses of the performance of individual patients have been undertaken (*see* Kinsbourne and Rosenfield, 1974; Hier and Mohr, 1977). There is only one example of an analysis of an agraphia syndrome using the approach developed for the study of the acquired dyslexias, that of Beauvois and Dérouesné (1981) on the writing of a patient whose acquired agraphia consisted of a specific difficulty in spelling those words which use any irregular or ambiguous phoneme-grapheme transformations, the writing of regular words and nonsense syllables being preserved. This analysis led to the isolation of an agraphia syndrome which appears to correspond to the syndrome of surface/semantic dyslexia well known in reading (*see* Marshall and Newcombe, 1973; Shallice and Warrington, 1980). Beauvois and Dérouesné (1981) argued that writing a word can be performed either by using a direct lexical method of obtaining its spelling (the 'lexical route') or by sounding-out the word into phonemes and employing phoneme-grapheme transformations (the 'phonological route'); their patient was held to have a specific deficit of the lexical route.

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The existence of a complementary difficulty, namely, a specific difficulty in transforming phonological information to an orthographic form, would speak to a long-standing dispute in the history both of the agraphias and of the normal spelling process. This concerns the role of phonological processing in writing. The orthodox position, that writing depends crucially upon phonological mediation or the roughly equivalent but vaguer 'inner speech', has been held by a number of authors in neurology, for instance, Wernicke (1874), Marie (1897) and Dejerine (1914, p. 138). This position can be held in either a weak or a strong form. In the weak form the nature of the mediating link is left unspecified, as in Geschwind's (1969) view that 'to write a word the spoken form must be aroused first'. In the strong form writing is held to depend upon segmentation of the spoken form at a phonemic level. For instance, Luria (1970) states that 'After evaluation of the speech sounds and recognition of the word, the next step toward writing the word is the coding of the sound units (phonemes) into the units of writing (letters).' The study of spelling errors in children has given rise to related views. Thus Frith (1980) argues that children's spelling normally involves three stages—first, a correct analysis of speech sounds into phonemes, secondly, the conversion of phonemes into graphemes and thirdly, the selection of conventionally correct graphemes out of all the phonetically plausible ones.

The main argument for the classical view stems from the association of writing disorders with particular forms of aphasia, particularly Wernicke's aphasia where Geschwind (1969) claims that writing disorders invariably exist. In fact Wernicke's aphasics do not always have as severe a deficit with writing as with speaking. Lhermitte and Dérouesné (1974), Hier and Mohr (1977) and Basso *et al.* (1978) have all described fluent aphasic patients whose writing was at the very least considerably better than their spontaneous speech. Moreover, Hier and Mohr (1977) point out that the normal association between writing and speaking in Wernicke's aphasia might well be a consequence of the lesions involved being of large size and therefore affecting multiple functional systems. The case of Hier and Mohr (1977), in particular, appears to present severe difficulties for even the weak version of the classical view. However, in the analyses of these patients the disorders of spontaneous speech were not analysed using an information-processing approach, so it is not entirely clear which sub-systems were in fact damaged, which is crucial for the argument.

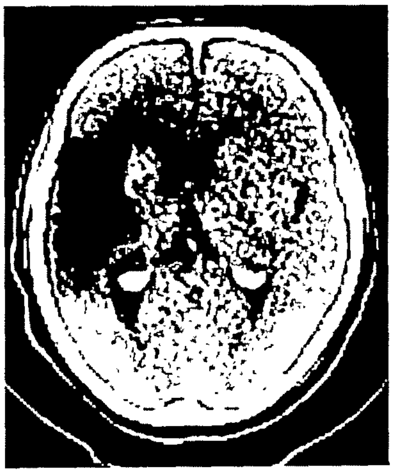

FIG. 1. CT scan of November 1979.

In the present paper the classical position is assessed from a somewhat different perspective, namely, how far the theory of phonological mediation can account for the particular pattern of difficulties in the writing performance of a patient with a very mild conduction aphasia. If the strong version of the classical theory were correct, then a patient who has a severe deficit in transforming phonemic information into a graphemic form should be almost incapable of writing. A patient with this deficit is described here and yet he has a remarkably spared writing capacity.

CASE REPORT

Four years before this investigation P.R. a right-handed computer salesman in his mid-fifties, had sustained an infarction mainly involving the territory of the left middle cerebral artery (*see* fig. 1). An angiogram performed at the time was reported as showing extensive internal carotid artery thrombosis originating at the bifurcation on the left side. He was unconscious for some weeks and had a severe expressive dysphasia and right-sided hemiplegia. On first admission to the National Hospital eighteen months later, his only neurological signs were numbness on the right side of the body and awkward movements of the right hand. On psychological testing at the time he had a Verbal IQ of 94 and a Performance IQ of 123. He had a speech disturbance characteristic of a conduction aphasic with mixed repetition and reproduction aspects (*see* Shallice and Warrington, 1977).

At the time of the investigation of his writing, his WAIS performance had improved to Verbal IQ 111 (all sub-tests being performed in the range from average to superior levels) and Performance IQ 127 (all sub-tests being performed at the superior or very superior levels). Digit span in particular had improved to 5, although the scaled score increase was mainly due to a change in backward span. Long-term memory functions were intact. On the recognition memory test of Warrington (1974) he scored within the average range, namely, 47/50 for words and 42/50 for faces. On the Boston Aphasia Test (Goodglass and Kaplan, 1972) he scored at ceiling or near-ceiling on all tests except repeating phrases (4/16), comprehension of oral spelling (2/8) and written formulations. He scored in the normal range on tests of auditory comprehension and naming—the

Peabody test (Dunn, 1965) (144/150), words from description (Coughlan and Warrington, 1978) (13/15) and object naming (McKenna and Warrington, 1980) (objects 26/30, proper names (24/30). Spontaneous speech was fluent with good word choice and only very occasional literal paraphasias; it was, however, very limited in variety of grammatical construction and poor in control of tense. On dichotic listening (3 digits to each ear) he scored 58/60 on the left ear and only 10/60 on the right. He could be classified as an almost resolved case of conduction aphasia. His aphasia was much less severe than would have been predicted on anatomical grounds. Most of the left hemisphere tissue classically associated with language including Broca's and Wernicke's regions had been damaged.

The findings of primary interest were those concerned with P.R.'s processing of the written word, particularly writing. His spontaneous writing was laboured and slow, both because of slight motor difficulties and difficulties of formulation. In twenty minutes he wrote a 154-word passage making 8 mistakes and in another such period he wrote (on a different subject) 157 words making 9 mistakes. Errors included omission of verbs, incorrect conjugation of verbs, and function word substitutions. On the Schonell reading test he scored at 90/100, equivalent to an IQ of 108 (Nelson and McKenna, 1975). In reading 337 low frequency words from the Brown and Ure (1969) list he made only 2 errors and in general read rapidly and effortlessly. On Schonell spelling he scored 83/100 printing and 72/100 spoken. He had no greater difficulty in writing in script than in printing. On 36 words of mixed frequency from the Brown and Ure (1969) list he scored 35/36 correct, both when writing in script and in printing. As printing is less ambiguous to score, it was used in all further investigations.

INVESTIGATION OF THE WRITING PROCESS

Nonsense Syllable Writing

The most striking aspect of P.R.'s writing difficulty was his inability to write nonsense syllables or nonsense words. On a number of occasions he attempted to write to dictation a set of such stimuli one at a time along with a set of words matched in their phonological structure; for instance, in one such pair of sets each set consisted of vowel-consonant(s) (VC) syllables with each vowel and consonant (or consonant cluster) used equally often in the two sets. P.R. was asked first to repeat the stimulus and then to write it. Table 1 gives the results of these tests.

TABLE 1. WRITING OF MATCHED WORDS AND NON-WORDS

	Writing				*Reading (twice)*	
	Word		*Non-word*			
	Rep.	*Write*	*Rep.*	*Write*	*Word*	*Non-word*
VC (20)	20	18	20	6	20	14
4-letter (10)	10	9	10	2	9.5	8
6-letter (10)	10	10	8	0	10	7.5
8-letter (10)	10	10	7	1	10	6.5

(Words failed: own, is, cope.)

He repeated nearly all the stimuli correctly but his writing of the nonsense syllables and non-words was extremely poor. Table 1 also shows his performance on reading the same set of stimuli on two occasions. He has a deficit on this task too, but quantitatively and qualitatively a much smaller one than in writing. For instance, his reading errors, unlike the writing ones, differed relatively little from the correct response, for instance *orch* read as /ɔːk/ and *ite* read as /ɪt/.

The production deficit was present whether the response was by writing or by spelling aloud. A set of 40 nonsense syllables (20 consisting of two phonemes and 20 of more than two) were dictated to him for writing together with a matched set of 40 for spelling aloud, order of presentation being balanced. In each case he was asked to repeat the nonsense syllable; on the rare trials on which any error occurred it was repeated again, and on all but one trial he then said it correctly. He then had to write or spell aloud. He wrote only 6/40 nonsense syllables correctly and spelled aloud only 4/40.

His ability to repeat the non-words shows that the difficulty cannot be attributed to a perceptual problem with non-words. However, as P.R. had been a conduction aphasic and had a span of only 5 digits, one obvious possibility is that he was unable to hold the nonsense syllable sufficiently well to transform it into a graphemic representation. It could be that while he is transforming the first phoneme, the others are forgotten. Such a mnestic account of his inability to write non-words was therefore tested. In three tests, he was presented auditorially with a nonsense syllable, asked to repeat it, then asked to write it, and at least ten seconds later asked to repeat it again. On all occasions, he performed significantly better on the second repetition than on writing the nonsense syllable (*see* Table 2). Thus even when he could not write nonsense syllables he could still repeat them. This shows that a difficulty in retaining the stimulus item cannot account for his failure to write non-lexical items.

Appendix 1 provides a corpus of the responses in the written conditions of two of the experiments on nonsense syllables (that is, including the VC and four-letter (nonsense) conditions of the first of the experiments). The errors that occur are very varied. Often he could not produce any written response that he felt was at all plausible and his substantive errors were frequently very different from the stimulus item. However, what is particularly interesting is that when he wrote a nonsense

TABLE 2. RECALL OF NONSENSE SYLLABLES AFTER AN ATTEMPT TO WRITE

	Immediate repeat	*Write*	*Later repeat*	*Sig.*
CV	17/20	6/20	13/20	0.05
CVC I	19/20	2/20	13/20	0.01
CVC II	20/20	8/20	20/20	0.01

Sig. is the significance level of the difference between writing and later repeat performance.
C = consonant. V = vowel.

syllable correctly, he frequently commented that he used a word as a mediator, for example, *sim→sym* (via *symbol*) or *jund→jund* (via *junta* and *junk*). Some errors showed this process of use of a mediator very clearly, for example, *sult→ault* (via *assault*), *fure→fi* (via *fjord*), *na→gn* (via *gnat*), *eft→de* (via *deft*), *eed→reed* (via *creed*) (some of the examples are from pilot experiments). Once the mediating word has been obtained and spelt he did not seem able to use the phonology effectively to provide an appropriate modification. The frequency of use of a mediator was not formally investigated, but it appeared that one was used on the great majority of trials on which the nonsense syllable was correctly written. There were, however, correct responses about which he explicitly denied using a mediator.

Word Writing

By contrast with his great impairment in writing nonsense syllables, P.R. had only a very slight difficulty in writing words. To obtain a more adequate baseline of his writing performance for individual words, a set with known concreteness and frequency ratings were used. From the Brown and Ure (1969) tables 622 words were dictated to P.R. He wrote 91.3 per cent of the words correctly. For high frequency words (A or AA) he wrote correctly 100 per cent of words above the median in concreteness and 92 per cent of those below the median. For lower frequency words, he wrote correctly 96 per cent of high-concreteness words and 80 per cent of low-concreteness words. Errors were of various types; an error corpus is given in Appendix 2. With the exception of a single mis-spelling error, all involved the production of another word, a type of error analogous to those characteristic of certain central dyslexic patients in reading. A classification quite similar to that used in the acquired dyslexias (*see* Marshall and Newcombe, 1973; Shallice and Warrington, 1975) can be made (*see* Table 3) and indeed the error pattern resembles that found in phonological alexia (*see* Beauvois and Dérouesné, 1979*b*; Patterson, 1981). The regularity of the phoneme-grapheme transformations involved had no effect on word writing; on the irregular words of Coltheart, Besner, Jonasson and Davelaar (1979) he scored at ceiling (38/39). His account of his ability to write words is of interest. He describes it as transcribing from an inner 'screen' on which he sees the word.

TABLE 3. ERRORS IN WRITING 622 WORDS FROM THE BROWN AND URE POOL

Mis-spellings	apprehension → apprension	1
Structurally similar	shy → shine	16
Derivational	spill → spilt	11
Mixed	salad → celery	3
Omission		23

The error types are explained in more detail in Appendix 2.

Patients with deficits of the phonological route in reading find function words especially difficult to read (*see* Marshall and Newcombe, 1966; Shallice and Warrington, 1975; Beauvois and Dérouesné, 1979*a*; Patterson, 1981). P.R. had no difficulty reading function words (70/70 correct), but it did seem possible that he might have a writing difficulty. Forty high-frequency words were dictated to him, on two different occasions. Half were content words and half function words. He performed almost perfectly on the content words but made numerous errors on the function words such as *any*, *than*, *indeed* and *with* (*see* Table 4). The difference in performance was significant on both occasions (Fisher Exact Test (i) $P < 0.05$,(ii) $P < 0.01$). On a third occasion he was asked to repeat a function word before attempting to write it. He repeated all 50 function words but failed to write 17 of them, showing that the specific function word difficulty cannot be attributed to a failure to perceive or retain the function word.

If the phonological route is not being used in writing, then it might be expected that articulatory suppression would not affect writing performance. P.R. was asked to write the names of presented pictures (for example, *trowel*, *candle*, *camel*) either in silence or while he continuously articulated 'Hiya'. He wrote 18/20 names correctly in silence and 19/20 correctly with articulatory suppression, and on only one occasion did he stop suppressing while writing. His writing was clearly not affected by articulatory suppression.

TABLE 4. WRITING PERFORMANCE ON HIGH-FREQUENCY CONTENT AND FUNCTION WORDS

	(i)	*(ii)*
Content words	20/20	19/20
Function words	15/20	10/20

The Operation of the Non-lexical Route

The most basic processes in the operation of the non-lexical route for writing would seem to be the segmentation of the utterance into a string of phonemes (or possibly groups of phonemes) and then the transformation of each of these units into its corresponding graphemic form. P.R. had a difficulty in the second of these processes and probably in the first of them too.

Considering the second of these processes, on two occasions 20 *sounds* conventionally associated with single letters (*e.g.* /bə/ for *B*; note *not* letter names) were dictated to him one per trial. He was very poor at writing the corresponding letter (*see* Table 5) and his errors were frequently failures to respond or totally incorrect letters (e.g. /nə/→*s*). He was also given a similar task in which 10 sounds corresponding to two letters (either single consonants such as *ch* or consonant clusters as *sp*) were dictated to him. Again he performed very poorly (*see* Table 5) and his correct responses nearly all involved the use of a mediating word, *e.g.* /klə/→ '*clutter*' → *cl.* Errors were normally a failure to respond. As a control he was dictated either one or two letter names; he had virtually no difficulty in this condition. An analogous dissociation between 'naming' and 'sounding' has already been observed in acquired dyslexia (*see* Shallice and Warrington, 1980).

TABLE 5. THE WRITING OF WORD COMPONENTS FROM THEIR DICTATED SOUNDS

Response		*Repeat*	*Write*
Single letter	I	19/20	11/20
	II	22/23	15/23
Two letters	I	10/10	3/10
	II	10/10	6/10

He also appeared to have a difficulty in segmentation. Baron, Treiman, Wilf and Kellman (1980) have devised a segment comparison task to test for segmentation ability; subjects are presented with two words visually for example (chord, cap) or (stage, fig) and have to decide whether the underlined letters sound the same in the two words. Given the complexity of English spelling, the only reliable way to perform this task is to pronounce each word, segment its sound into phonemes, determine which of these phonemes corresponds to the underlined letter(s) and then judge whether the critical phonemes in the two words match. P.R. scored 85/120, 94/120, 89/120 on three separate occasions (he made only one minor error in reading the 240 words aloud); his average error rate of 26 per cent is nearly double that of the mean of Baron *et al.*'s subjects (14 per cent). Moreover he performed the task very slowly. When asked merely to sound each underlined letter or letter-combination as it would be sounded in that word—a task that also involves segmentation—he scored 189/240 (21 per cent errors) and complained that he found the task extremely difficult. Segmentation skills were not totally absent. On a test of giving the number of syllables in a word he was correct on 18/20 occasions. On the Auditory Analysis Test of Rosner and Simon (1970) which involves the subtracting of a given phoneme or syllable from a word (*smile* – /s/) and producing the remainder ('mile') he was correct on 14/40 trials. Finally on the least demanding test of all judgement of whether two visually-presented words rhyme, using the stimuli of Coughlan and Warrington (1978), he performed nearly perfectly (95/96). However, when simply asked to sound out a word slowly so that all its constituent sounds were distinct, as in *cat* → '/k/ . . . /æ/ . . . /t/', he appeared to understand the task and yet claimed he found it exceptionally difficult; he scored 0/10. Overall it appears that segmentation skills were sufficiently impaired as to seriously hamper spelling by a non-lexical method.

Comprehension and Writing

On a number of occasions in attempting to write abstract words, P.R. initially appeared to be unable to understand the word—a very mild auditory-verbal agnosia; he was also unable to write it. On some of these occasions, however, comprehension of the word appeared to occur suddenly somewhat later and he was then immediately able to write it. It appeared that in order for him to write the word merely dictating it to him was insufficient; he needed to access its meaning. To test whether his ability to write a word was indeed dependent upon his being able to access its meaning the following experiment was performed. He was presented auditorially with 80 low-frequency abstract words (for example, *amenable*, *entity*, *habituate*) and asked first to repeat them, then to write them and finally to give an account of their meaning. Two independent judges assessed his ability to give an adequate explanation of the meaning. He was less able to write words whose meaning at that particular time he could not explain (*see* Table 6); there is a contingency coefficient of 0.33 between grasp of meaning and ability to write the word, significantly different from 0 ($P < 0.02$). The words which he could neither write nor explain were not outside his vocabulary, as on other occasions he could either write them or explain their meaning. However, as these words were low in their frequency of occurrence in English, it might be argued that some were near the limit of his vocabulary, and that this sub-set might, for reasons unrelated to his particular cognitive difficulty, be expected to provide difficulties for both writing and explanation. The correlation might not therefore reflect a causal dependency between processing stages in the writing process.

A related test was therefore devised using function words which are of a much higher frequency, and for which this artefactual explanation of association between the variables would not apply. For 100 function words he was first asked to repeat the dictated word, which he always did correctly. He was then asked to write it and whether he succeeded or not, he was asked to produce a novel sentence with the word used appropriately. His responses were divided into 'appropriate', 'inappropriate' or 'total failure'. A response was considered 'appropriate' if there was semantically appropriate use of the function word even if there was an error

TABLE 6. WRITING AND EXPLAINING MEANING OF ABSTRACT WORDS

	Writing of word	
	Correct	*Incorrect*
Meaning grasped well	21	3
Meaning possibly or partly grasped	24	9
Meaning not grasped at all	6	8

The results for the 71 words that were correctly repeated. For a 'meaning' response to be entered in the first or third category, both judges had to be in agreement, giving on a 3-point scale 2 or 3 in the former case and 0 in the latter.

in the rest of the sentence. Thus for *anybody* the response 'Anybody that can sing, you must sing in the hall for your supper' was accepted as appropriate, but for *whether* (correctly written) 'Whether or not with the slings and arrows, I had a crushing blow on May 23rd' was considered inappropriate; for the 'total failures', he would say he had no idea of the meaning of the word. The contingency coefficient between his being able to use the word appropriately and his being able to write it was 0.49 significantly different from 0 ($P < 0.01$) (*see* Table 7). A similar result was obtained in another experiment using 50 words. Thus there seems to be a clear relation between his ability to understand a word on a particular occasion and his ability to write it.

TABLE 7. WRITING AND USE OF 100 FUNCTION WORDS

		Writing of word	
		Correct	*Incorrect*
Use of Word	Appropriate	70	5
	Inappropriate	11	3
	None	3	8

DISCUSSION

The main characteristic of P.R.'s writing performance is the dramatic dissociation between his relatively well preserved ability to write words and his virtually total inability to write nonsense syllables or nonsense words. Thus when matched sets of words and nonsense material were used, he wrote 94 per cent of the words correctly, compared with only 18 per cent of the nonsense material. By contrast, 12-year-old normal spellers have virtually no difficulty spelling non-words (Frith, 1980). Moreover, when nonsense material was written correctly, this nearly always depended upon P.R. using his knowledge of the spelling of a related word as a mediator.

A somewhat greater difficulty in writing nonsense syllables than words is not infrequent in patients with left hemisphere lesions. Dubois (1977) observed such an effect in 17/61 patients with lesions involving the left temporal lobe. What is critical about the finding of a very large effect in P.R. is that it can be shown not to be secondary to a failure to retain the nonsense syllable or nonsense word. This follows primarily from his ability to repeat nonsense syllables after he has failed to write them. In addition the two operations which appear to be basic to the writing of nonsense syllables—the segmenting of the overall sound into smaller units and the writing of individual speech sounds—were both impaired.

Two factors which did not greatly influence his performance were whether the response was written or spoken and the form of the orthographic code used, script or print. The latter contrast had no effect. There was a small superiority of written spelling over spoken spelling, but this occurs quite generally in agraphia (*see* Wapner and Gardner, 1979) and it is probably to be expected in a patient with a limited span. The fact that P.R.'s writing performance is insensitive to these variables suggests that his deficits lie high in the writing system, where high/low is used in the sense of more/less central. In the terminology of Shallice and Warrington (1980) his writing deficit corresponds to a central dyslexia and not to a peripheral dyslexia.

The writing dissociation in P.R. complements that observed by Beauvois and Dérouesné (1981) of a patient who could write nonsense syllables well but not irregular words or those words which involve phoneme–grapheme transformations that are highly ambiguous. The existence of the double dissociation strongly suggests that in an analogous fashion to reading, writing can be performed by more than one set of operations (that is, at least two routes) as already assumed by some authors for normal writing, (*see* Baron *et al.*, 1980; Morton, 1980). Wapner and Gardner (1979) on the basis of a group study have also argued for different spelling strategies being used by different patients, in their case between those with anterior as opposed to posterior left hemisphere lesions; however, their critical error analysis is subject to other interpretations such as a difference in the level of the writing system at which the deficit occurs. The differentiation between two writing routes does, though, probably correspond to that made by Sasanuma and Fujimura (1972) for Japanese, namely, that kanji (non-phonological) and kana (phonological) writing involve different processing modes and that these can be differentially impaired in neurological patients. I will use the terms 'phonological' and 'lexical', respectively, for the routes presumed to be impaired and intact in P.R. The existence of a route not involving phoneme-grapheme transformations is, of course, in direct conflict with the strong form of the classical theory.

The dissociation in P.R.'s writing between intact processing by the lexical route for most classes of words and the gross impairment in the use of the phonological route is analogous to that found in the acquired dyslexic syndrome of phonological alexia (Beauvois and Dérouesné, 1979*a*,*b*; Shallice and Warrington, 1980; Patterson, 1981). In addition, the types of writing error found in P.R., particularly structurally-similar errors and derivational errors, appear to correspond to the visual and derivational errors found in phonological alexia. Moreover phonological alexic patients frequently have specific difficulty with function words (Beauvois and Dérouesné, 1979*a*; Patterson, 1981), although this is not always the case with such patients. A specific deficit of function word writing occurs in P.R. Thus there is a striking correspondence between the acquired dyslexia syndrome, phonological alexia, and P.R.'s difficulty, which I will call phonological agraphia.

P.R. also had a mild phonological alexia. His reading of nonsense syllables and nonsense words was slightly impaired. The deficit was, however, both qualitatively and quantitatively less severe than the writing deficit. It is probably incorrect to interpret P.R.'s difficulties as reflecting damage to a phonological route common to both reading and writing, which is the more 'stressed' by the writing process.

Beauvois and Dérouesné's (1979*a*, 1981) patient R.G. showed a dramatically different dissociation with nonsense writing being intact and nonsense syllable reading being very impaired. The double dissociation strongly suggests that the phonological routes for reading and writing are distinct.

Of those patients previously described, Hier and Mohr's (1977) patient, A.E., is the one in whom there is strongest evidence that only the lexical route is being used. A.F. had fluent empty spontaneous speech and the absence of literal paraphasias and neologisms suggest that his deficit lay high in the speech production system. As he was almost totally unable to name objects orally it would appear that little information could reach the phonological route let alone be transmitted by it. Yet A.E. was able to write correctly 19/50 high-frequency names of objects presumably using the lexical route. This writing performance is, though, very much worse than that of P.R.

In view of the existence of preserved writing by the lexical route in P.R. for most classes of words, the most plausible view is that the lexical writing route was impaired in A.F. even though it could be partially used P.R. was indeed much less generally impaired than A.F. Moreover A.F. made many mis-spellings which involved both incorrect letters and a phonological mismatch with the stimulus word, for example, *elephant → elpanch*, a class of error virtually never observed in P.R., although frequently observed in agraphic spelling, (*see* Wapner and Gardner, 1979), and which might well indicate the use of a defective lexical route. An alternative view would, however, be that great individual differences exist in the capacity of the lexical route across normal subjects and that P.R.'s purely orthographic knowledge was particularly good, as his imagery of use of a television screen might suggest.

One piece of evidence that suggests that P.R.'s ability is not in some way special is the striking correspondence between the type of errors he makes in word writing and the 'slips of the pen' observed by Ellis (1980) in a large corpus of errors of a normal subject. In Ellis's corpus one type of error involved the writing of a word different from the intended one. The most frequent class of such lexical substitutions Ellis termed 'completion errors' such as *worms → words*. These correspond to the majority of the errors I termed 'structurally similar'; they have also been observed by Wapner and Gardner (1979) in other agraphic patients. Three-quarters of such errors in Ellis's corpus involved words with a common stem (for example, *possibly → possible*) or involved function words, for example, *of → or*. Hotopf (1980) has also shown that function word errors or common stem errors are particularly likely to occur in normal writing. These correspond to derivational errors and to the specific difficulty with function words observed in P.R. The similarity in pattern between P.R.'s errors and the lexical errors in Ellis's corpus suggests the use of a common mechanism in the two situations, namely, excessive reliance on the 'lexical route', in one case because of necessity and in the other for speed. This makes it more likely that P.R.'s lexical route does not operate in an atypically efficient fashion.

In writing by the lexical route the spelling of a word would be derived from a store containing complete orthographic information at an abstract letter level about how the word should be written. Such a store has been termed by Morton (1980) a 'graphemic output logogen'. Moreover, information in the store would be accessed entirely by lexical processes, not, for instance, by use of phoneme-grapheme transformations. Morton has argued theoretically that there are two different means by which such information might be accessed. One would be directly from semantic systems, the other from a store containing the specifications of the overall phonology of a word, his 'articulatory output logogen'.

Does P.R.'s deficit throw any light on the relative contributions of these two methods of accessing information in the graphemic output logogen? If the orthographic specification of a word were normally accessed only from the specification of its overall phonology, one has a version of the weak form of the classical theory. Phonological mediation would be crucial, but in terms of the specification of the word as a whole, not at the level of phonemes. There is some suggestion from P.R.'s writing performance that even this weak form of the classical theory is inadequate. In principle, information about the overall phonological specification of a word can be accessed in word repetition without the involvement of semantic systems; in Morton's (1980) terminology information can flow *directly* from the auditory input logogen to the articulatory output logogen. Moreover this does appear to happen in verbal associative agnosia when semantic representations cannot be adequately attained (*see* Warrington, 1975). Thus on this weak form of the classical theory, a patient with a verbal associative agnosia should be able to write to dictation a word that *can* be repeated even if he or she *fails* to understand the word. P.R. did have a mild associative agnosia. In his case, however, his ability to write a word seemed to depend heavily on his ability to understand it; in other words correct repetition alone was not sufficient to allow writing to occur. This suggests that a direct connection does exist between semantic systems and writing systems, as previously argued by Hier and Mohr (1977), and that the specification of the overall orthography of the word (the graphemic output logogen) can indeed be accessed directly from the semantic representation of the word. If P. R. relies, at least partially on, this route then when he cannot understand a word that he can repeat, he should have difficulty in writing it.

However, if one considers the complexities to which discussions of the relation between the acquired dyslexias and the detailed architecture of the reading system give rise (*see* Morton and Patterson, 1980; Schwartz, Saffran and Marin, 1980; Shallice and Warrington, 1980) it is probably premature to do more than tentatively speculate on such an issue in the much less well understood area of writing disorders. The more basic point remains that writing deficits appear to give rise to syndromes very analogous to those recently much studied in the acquired dyslexias, and that remarkable sparing of 'lexical route' writing can occur with the phonological route inoperative.

SUMMARY

A new agraphia syndrome is described in which the patient can write certain classes of words virtually perfectly but is very poor at writing non-words. It is shown that this difficulty cannot be explained by perceptual or memory problems. A number of aspects of the syndrome are shown to correspond to those of phonological alexia within the acquired dyslexias. It thus appears that agraphia syndromes can be analysed by methods analogous to those recently developed for the study of the acquired dyslexias.

ACKNOWLEDGEMENTS

I am grateful to Dr R. T. C. Pratt for permission to investigate his patient and report my findings and to Dr E. K. Warrington for her advice and for providing the facilities which enabled the investigation to be carried out. I should like to thank Ms R. McCarthy and Mrs M. Galton for their assistance with some of the testing and analysis, Dr Pratt, Dr E. M. Saffran and Dr Warrington for their comments on earlier drafts of the paper, and Dr A. M. Whiteley for his advice on the site of the lesion. I should also like to acknowledge the support of the Medical Research Council of whose Applied Psychology Unit I am a member.

APPENDIX 1. WRITING NONSENSE SYLLABLES

The nonsense syllable writing responses summarized in Tables 1 (except 6 and 8 letter sets) and 2 are listed below. Any written response which could be pronounced as the stimulus was considered correct. Those stimuli for which P.R. felt unable to make any reasonable guess are listed as *Omissions*. In brackets are any mediating words he stated he used (or comments about them). A word incorrectly repeated initially is indicated by * and one incorrectly repeated after an attempt to write by **.

VC (October 30, 1979)
Correct: *obe*, *ish* (‘*isthmus*’), *uke* (‘ukelele’), *arn* (‘barn without b’), *eft* (‘left’), *osk* → *osc* (‘oscograph’)
Omissions: *ole*, *aith*, *ex*
Errors: *ite* → *hight*, *ag* → *ra* (‘raj’), *ome* → *obel*, *ess* → *seve*, *aist* → *acet*, *eand* → *een*, *oalf* → *olf*, *ap* → *apt*, *eed* → *reed* (‘creed’), *orch* → *orc*, *ald* → *oud*

Four Letter Non-words (October 30, 1979)
Correct: *hile*, *rike* → *reich*
Errors: *pive* → *sp*, *sare* → *sev*, *slun* → *thun*, *thed* → *fed*, *fabe* → *sp*, *urch* → *urc* (‘urchin’), *jile* → *gyro*, *flot* → *floc*

CV (June 6, 1979)
Correct: *fi**, *ji* (‘Hindustani’), *na*, *je*, *sa*, *li*
Omissions: *ke*, *wa*, *ro***, *va***, *za*, *pe***, *ya*, *vi***, *gu**, *se*, *mi*, *vo*, *ja*
Errors: *bo* → *ba*

CVC I (June 6, 1979)
Correct: *sim* → *sym* (‘symbol’), *bup* (‘Bupa’)
Omissions: *tib*, *dep***, *cezz*, *kig*, *yut**, *zop*, *fup*, *rezz*, *tull*, *nid*, *cozz*
Errors: *woff*** → *wa*, *gam*** → *gammon*, *fem*** → *fe*, *div*** → *di*, *wib* → *whi*, *cuv* → *cup*, *vem*** → *ver*

CVC II (August 16, 1979)
Correct: *yut*, *fem*, *div* (‘dividend’), *sim* (‘simpatico in Spanish’), *rezz* → *res* (‘reservation’), *nid* (‘A nest in French’), *cozz* → *koz* (‘no special way’), *vem* (‘venom and exchanged last letter and middle one’)
Omissions: *tib*, *dep*, *kig*, *gam*, *zup*, *fup*
Errors: *woff* → *waf*, *cezz* → *sem*, *wib* → *wisp*, *cuv* → *cov* (‘covey’), *tull* → *talp* (‘talc’), *bup* → *coz*

APPENDIX 2. ERRORS IN WRITING WORDS

The errors made in writing the Brown and Ure words are:

absorption	→ *absolve*	(SS)
anxiety	→ *anguish*	(Mixed)
apprehension	→ *apprension*	(Mssp.)
ascend	→ *ascent*	(Der.)
big	→ *pig*	(SS*)
chore	→ *shore*	(SS*)
custom	→ *custard*	(SS)
defect	→ *defection*	(Der.)
definite	→ *definition*	(SS)
depressed	→ *depress*	(Der.)
famous	→ *fence*	(SS)
fear	→ *beer*	(SS*)
hatred	→ *hateful*	(Der.)
injure	→ *injury*	(Der.)
loveliness	→ *lovely*	(Der.)
misfortune	→ *misfortunate*	(Der.(?))
mitten	→ *mittens*	(Der.)
navigation	→ *navigator*	(Der.)
obtain	→ *opportune*	(SS)
occurrence	→ *concurrent*	(Mixed)
plum	→ *thumb*	(SS*)
quart	→ *caught*	(SS*)
salad	→ *celery*	(Mixed)
shy	→ *shine*	(SS)
silly	→ *sea*	(SS)
soothe	→ *sooth*	(SS)
spill	→ *spilt*	(Der.)
suicide	→ *sea-side*	(SS)
supplicate	→ *supplement*	(SS)
truth	→ *true*	(Der.)
wild	→ *wide*	(SS)

Mixed errors are errors which are *both* structurally and semantically related to the stimulus (*see* Shallice and McGill, 1978). Eleven of the Structurally Similar errors are of the sort Ellis (1980) called completion errors. Five of the Structurally Similar errors marked (SS*) appear to arise from a phonological source. As P.R. did not have to repeat the words before writing them, he might have misperceived these five. A second corpus from the 'abstract word' experiment in the Comprehension and Writing section together with a replication of that experiment is therefore provided. All errors arose from correctly repeated words except for the two marked (**), on one of which an (SS*) error did in fact occur.

abase	→ *obeise*	(Mixed)
amenable	→ *ameliorated*	(SS)
coherent	→ *incoherent*	(Der.)
concomitant	→ *concommitant*	(Mssp.) (twice)
correlate	→ *collarate*	(SS(?))
deprecate	→ *deprecation*	(Der.)
derivative	→ (i) *derivement*	(Der.)
	(ii) *divertiment*	(SS and Mssp.)
effusive*	→ *suffused*	(SS*)
obtrusive	→ *obstruct*	(SS)
preponderance	→ *perponderance*	(Mssp.)
profligate	→ *profligaty*	(Der.(?)) (twice)
querulous**	→ *quarrelous*	(Mixed)
restitution	→ *retribution*	(Mixed)
strata	→ *strato*	(Der.(?))
tirade	→ (i) *irate*	(Mixed)
	(ii) *tyrrate*	(Complex)

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ELECTROPHYSIOLOGICAL STUDIES OF GAIT IN SPASTICITY AND RIGIDITY

EVIDENCE THAT ALTERED MECHANICAL PROPERTIES OF MUSCLE CONTRIBUTE TO HYPERTONIA[1]

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INTRODUCTION

IN a previous study we examined the importance of preprogrammed muscle activity, stretch-related muscle activity and intrinsic mechanical properties of muscle for the control of ankle angle during running in normal human subjects (Dietz, Schmidtbleicher and Noth, 1979). In the present study we have examined patients with spasticity or parkinsonian rigidity with the aim of finding a physiological mechanism in terms of altered patterns of muscle activity to account for the disturbed pattern of locomotion. Another extensive study on motor control during locomotion in hemiparetic patients has described three different types of disturbed muscle co-ordination (Knutsson and Richards, 1979). Correlation of these three groups of abnormal patterns of leg muscle activity with typical clinical signs was obviously difficult. This study is concerned with the pathophysiology of increased muscle tone, that is, enhanced resistance to muscle stretch in patients with spasticity and parkinsonian rigidity. The nature of the pathophysiological basis of muscle hypertonia has not been much elucidated since Romberg's suggestions (1851) of a generally enhanced activity of spinal nerve cells in these diseases. However, in the few electrophysiological studies of natural movements in these patients, no such enhanced muscle activity was observed (Altenburger, 1937; Knutsson and Richards, 1979).

Clinically, the spastic signs are usually exaggerated when patients are standing or moving. Therefore, the analysis of the innervation and co-ordination of the leg muscles was performed during a slow gait. From the innervation pattern obtained

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[1] The work was supported by the Deutsche Forschungsgemeinschaft (SFB 70—Hirnforschung und Sinnesphysiologie).

in patients with upper motor neuron lesions and parkinsonism it is concluded that changes occurring in the muscle fibres, and not in the muscle activity itself, must be mainly responsible for the increased muscle tone in both groups of patients.

METHODS

Patients and General Procedures

In 20 normal subjects, 10 spastic patients and 10 patients with Parkinson's disease the leg muscle EMG and changes in knee and ankle joint were examined during walking on a treadmill at a speed of 2 km/h. The age of the normals ranged between 14 and 74 years (mean 41 years); of the spastic patients, 31–66 (mean 46 years); and of the parkinsonian patients, 49–73 (mean 66 years). Muscle hypertonia, in terms of a raised resistance to slow passive stretch, was the predominant clinical sign in our selected group of patients. They were able to walk at a speed of 2 km/h. The spastic patients mostly complained about a long-lasting stiffness in the leg muscles, caused by a chronic lesion of the spinal cord, often at a cervical level. Most of the patients therefore had spastic signs on both legs, while the muscle paresis and the sensory deficits were of minor importance in the clinical examination (*see* Table 1). In the selected parkinsonian patients rigidity and akinesis were the predominant features. Most of them were pre-treated with L-dopa and/or anticholinergic drugs (*see* Table 2).

Electrical activity of mm gastrocnemius and tibialis anterior was recorded during maximal voluntary isometric contraction and at a force level of 5 kg before recording during locomotion.

TABLE 1. PATIENTS WITH SPASTICITY

Pat.	*Age (yrs)*	*Sex*	*Diagnosis*	*Duration of illness (yrs)*	*Appearance of spasticity*	*Impairment of walk*	*Reflexes*	*Other neurological features*	*Medication*
1	60	F	Post-op. meningeoma D8	1	Spastic paraparesis (R > L)	Slight	+ + + Bab.0	Slight sensory disturbance D10	None
2	42	M	Cervical myelopathy	1.5	Spastic tetraparesis (R > L)	Serious	+ + + Bab. +		None
3	64	M	Funicular spinal disease	2	Spastic ataxic paraparesis	Serious	0 Bab.0	Slight sensory neuropathy	Cyanocobalamin
4	37	M	Spastic paraplegia of unknown origin	12	Spastic tetraparesis	Serious	+ + + Clonus		Dantrolene
5	64	M	Cervical myelopathy	5	Spastic tetraparesis (R > L)	Serious	+ + + Bab. +	Slight disturbance of vibration sense[1]	Baclofen
6	41	M	Cervical myelopathy	0.5	Spastic tetraparesis	Slight	+ + + Bab. + Clonus	Slight distal sensory neuropathy[2]	None
7	31	M	Amyotrophic lat. sclerosis	1.5	Spastic tetraparesis (R > L)	Serious	+ + + Bab. +		None
8	38	M	Multiple sclerosis	0.5	Spastic paraparesis (R > L)	Slight	+ + + Bab. + Clonus		Baclofen
9	55	F	Multiple sclerosis	15	Spastic tetraparesis (L > R)	Slight	+ + + Bab. +		Baclofen
10	43	M	Tuberculous meningitis	18	Spastic paraparesis (L > R)	Slight	+ + + Bab. +	Slight sensory disturbance and ataxia[3]	None

[1] Probably caused by posterior column lesion. [2] Diminished sensitivity to touch on the feet caused by toxic lesion by alcohol. [3] Funicular lesion, probably by post-inflammatory adhesions.

The latter was performed by holding a spring scale which was tied across the metatarsal bones of the foot. Normally this was done with the leg extended (knee angle 180 deg) and the ankle joint in a mid-position when no resting activity was present in the leg muscles (about 110 deg). It was already obvious from the clinical test that in patients with hemispasticity the tension of the Achilles tendon developed during passive dorsiflexion of the foot was much higher in the spastic leg than the normal one.

During locomotion patients were asked to walk as normally as possible and only with minimal support when necessary. Joint angle changes at the ankle and in a few subjects also at the knee were recorded by a potentiometer. The instants of contact of the heel and the ball of the foot with the ground were indicated separately by electrical switches fixed in the shoes. The sensitivity of these switches was 3 to 4 kg.

EMG Recordings and Analysis

The EMG of the medial head of gastrocnemius and tibialis anterior of one or both legs, and, in some subjects, that of the soleus also, was recorded with surface electrodes. The EMG was registered by a telemetric device (Schwarzer model 4024 FS) and filtered (time constant 3 ms). The EMG together with the signals of goniometers and electrical switches were transferred to a tape recorder (Tandberg series 115) and also, for artifact control, to a direct ink recorder (Siemens, type EM 34). It was ascertained that mechanical artifacts were minimal by passively shaking the leg and quickly extending the foot of the relaxed leg. Muscle electrical activity was analysed further off-line in a way described previously (Dietz *et al.*, 1979). The rectified EMG of 30 step cycles was averaged (Nicolet model 1072) using the electrical switch as trigger indicating the moment of ground contact. Goniometer signals were averaged in the same way. The resolution of the averager amounted to 1024 points for each step cycle. Averaged EMG records were also smoothed digitally $(X\bar{n} = \frac{1}{4}X(n-1) + \frac{1}{2}Xn + \frac{1}{4}X(n+1))$, which means that each of the 1024 points (Xn) was approximated to its adjacent points $(X_{(n-1)}; X_{(n+1)})$. To make comparison easier, all records were normalized on a time scale equal to one step cycle. To summarize changes in muscle electrical activity and the associated changes in ankle joint in normal subjects, and to compare these with values obtained in patients the mean values of EMG strength and goniometer signals were determined for each group of patients. The sampling interval for the calculation of the mean values with standard deviations was 1/20 of one step cycle.

TABLE 2. PATIENTS WITH PARKINSON'S DISEASE

Pat.	*Age (yrs)*	*Sex*	*Duration of illness (yrs)*	*Impairment of walk*	*Rigor*	*Tremor*	*Hypokinesia*	*Reflexes*	*Other neurological features*	*Medication*
1	62	M	3	Serious	+	+	++	++	Slight disturbance of vibration sense[1]	L-dopa + benserazid, biperidin
2	50	F	1	Slight	(+)	(−)	(+)	+		None
3	74	M	10	Slight	+	+	+	++		Amantadin
4	76	M	5	Serious	++	+	+++	++	Slight neuropathy[2]	Biperidin
5	72	F	1.5	Serious	+	+	+	+		L-dopa + benserazid, amantadin
6	68	F	5	Slight	+	+	(+)	+		L-dopa + benserazid, amantadin
7	71	F	9	Serious	+	+	++	+++ Clonus		L-dopa + benserazid, biperidin
8	64	M	8	Slight	(+)	+	+	+++		L-dopa + benserazid
9	64	F	19	Serious	+	+	+++	(+)		Carbidopa + L-dopa, biperidin, amantadin
10	56	F	18	Serious	+	+	++	+		L-dopa + benserazid, amantadin

[1] Probably due to vascular funicular lesion.

[2] Diminished sensitivity to touch on the feet caused by chronic nephropathy.

RESULTS

Leg Muscle Activity in the Gait of Normal Subjects

Fig. 1 shows electrical activity recorded from mm tibialis anterior, gastrocnemius and soleus, with the signals of the electrical switches indicating heel and ball contact, and the goniometer recordings indicating changes in ankle and knee joint angle in a normal subject walking at 2 km/h. There was no significant preinnervation of the leg extensor muscles before ground contact. In the stance phase, the electrical activity persisted during the period of passive dorsiflexion of the foot, indicated by the ankle goniometer. At the beginning of plantar flexion, the EMG of gastrocnemius decreased and that of tibialis started already at the end of the stance phase. As can be seen from the ankle goniometer signal, the foot is dorsiflexed during the swing phase by a relatively small activity of tibialis. In most cases the tibialis EMG persisted until the beginning of the stance phase or it was divided into two EMG peaks, the second peak arising at the end of the swing phase.

Fig. 2 shows the normalized averaged records obtained from all 20 normal subjects (24 legs investigated). While the amplitude of the recorded leg muscle

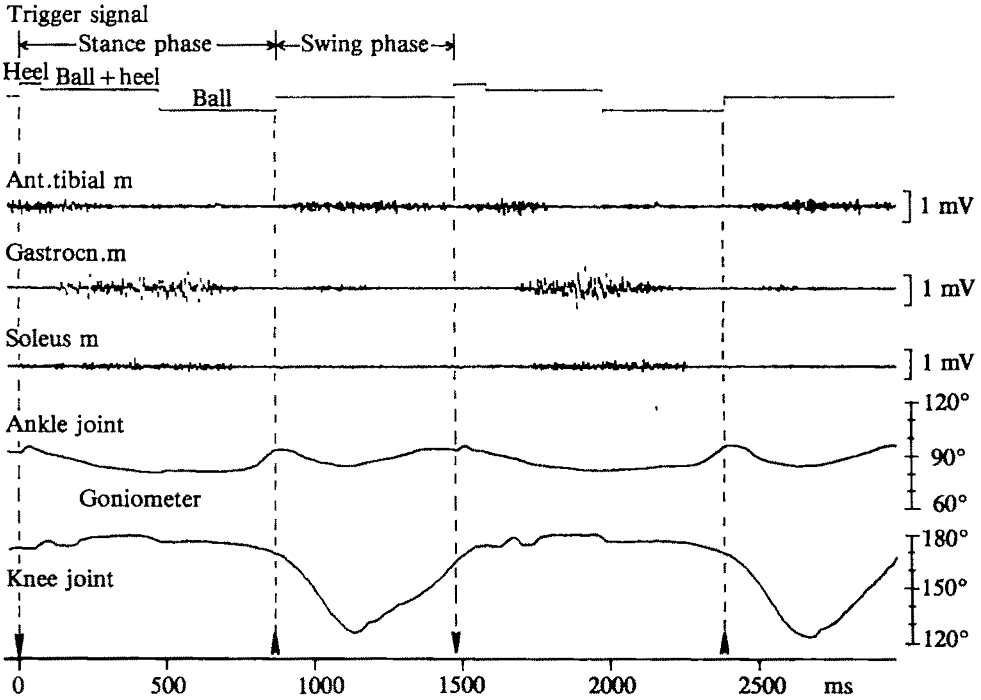

FIG. 1. Typical original recording of two step cycles from a normal subject during slow gait. *From top to bottom:* electrical switch signals (trigger) from the heel and the ball of the foot; tibialis anterior, soleus and gastrocnemius EMGs; and goniometer signals of angles of ankle and knee joints. Vertical lines indicate touch down (↓) and lift up (↑) of the foot.

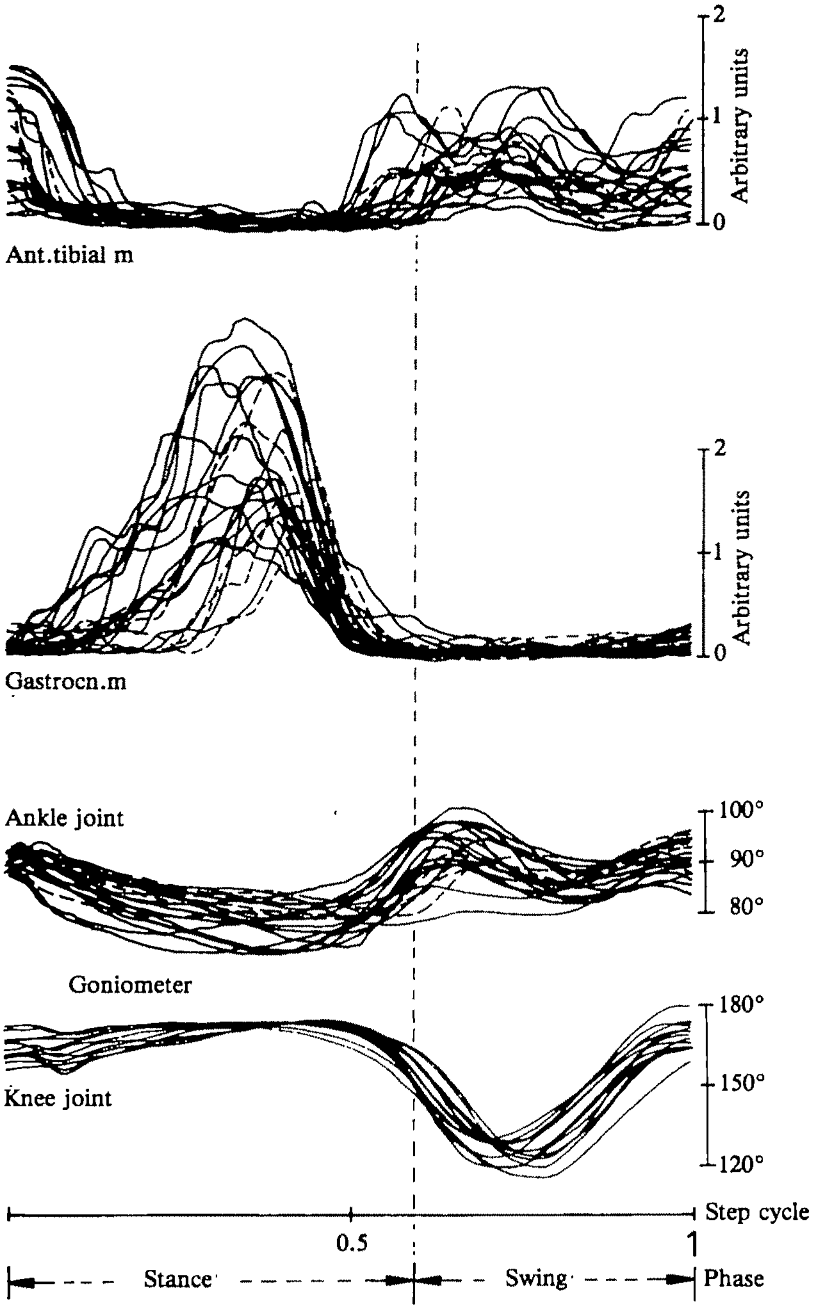

FIG. 2. Normalized histograms obtained in 20 normal subjects (24 legs examined) during slow gait. *From top to bottom:* rectified and averaged tibialis anterior and gastrocnemius EMGs (n = 30 step cycles/each subject); goniometer recording of ankle and knee joint angles (n = 12). The broken lines are recordings taken from elderly normal subjects (above 60 years old). Vertical line indicates the end of stance phase.

EMG signal varies from subject to subject, the same reciprocally organized timing of antagonistic muscle activity was observed in all subjects as well as a close correlation with the excursions of the ankle joint. There was no difference in the timing or strength of the recorded electrical activity of the leg muscles between older and younger people. Repetitive tests in the same subject showed less than 10 per cent variation in the amplitude of recorded electrical activity.

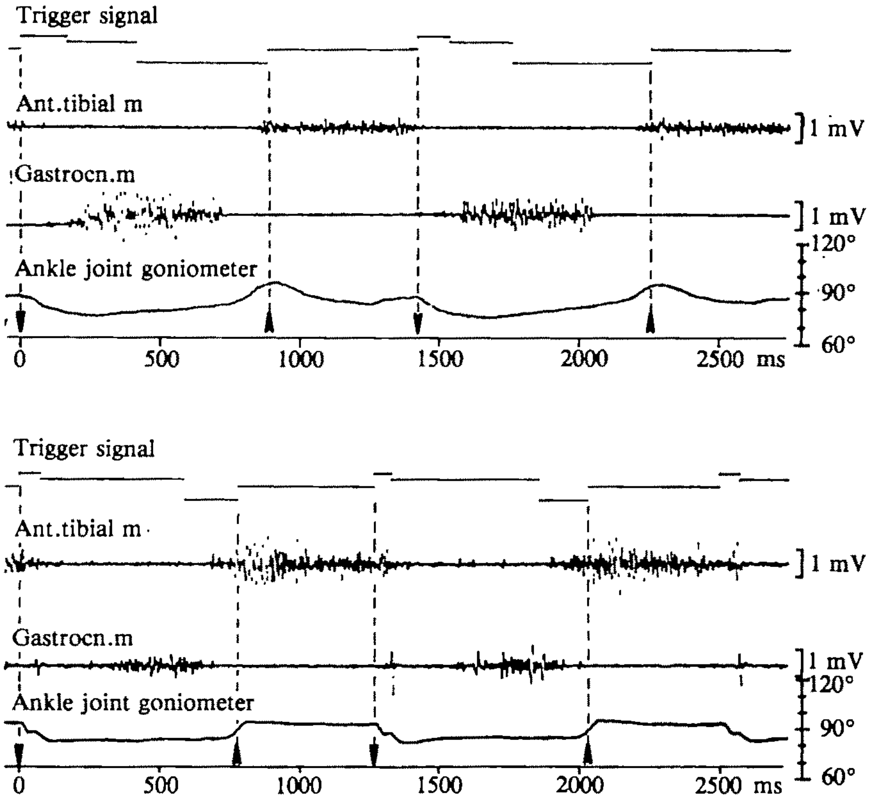

FIG. 3. Original recordings from a normal subject (*above*) and a patient with spastic legs (*below*). The raw EMGs from tibialis anterior and gastrocnemius muscles together with the trigger and goniometer records of ankle joint angle are shown in both subjects. The different phases of the gait cycle are indicated by the trigger signal and the vertical lines (*see* fig. 1).

Pattern of Muscle Activity Recorded in Spastic Patients

Fig. 3 demonstrates the typical EMG recordings from tibialis anterior and gastrocnemius muscles, together with the signal from the goniometer measuring ankle angle in a normal subject and in a patient with spastic paraparesis. While the timing and strength of the gastrocnemius EMG during the stance phase of gait are quite similar in both cases, the amplitude of the tibialis EMG is much stronger in the spastic patient. The goniometer record from the ankle joint indicates that this tibialis EMG, in contrast to that of the normal subject, is not accompanied by dorsiflexion of the foot during the swing phase. This cannot be explained on the basis of activity in antagonistic muscles opposing dorsiflexion of the foot, because gastrocnemius is essentially inactive at this time. It could be argued that activity in soleus muscle during the swing phase might be responsible for opposing the activity of tibialis and preventing dorsiflexion in spastic patients. In some normals (2) and patients (4) the EMG of the medial part of soleus was, therefore, recorded together with the gastrocnemius EMG. Soleus activity parallels activity in gastrocnemius in patients as well as in the normal subjects and, therefore, would not account for the lack of dorsiflexion of the foot. Also recordings with needle electrodes in gastrocnemius and soleus muscles, performed in 2 patients, showed no difference to these results.

The relationship between the force developed in voluntary dorsiflexion and the amplitude of the EMG of tibialis anterior was the same for normal and spastic subjects. No significant difference could be found between the amplitude of tibialis activity recorded in the two groups while maintaining an isometric tension of 5 kg against a spring scale (*see* Methods) (normal subjects 1.9 mV ± 0.7; spastic patients 1.8 mV ± 0.6).

Fig. 4 demonstrates the average change in tibialis anterior and gastrocnemius EMG activity as well as in angle of ankle and knee joint of a healthy and a spastic

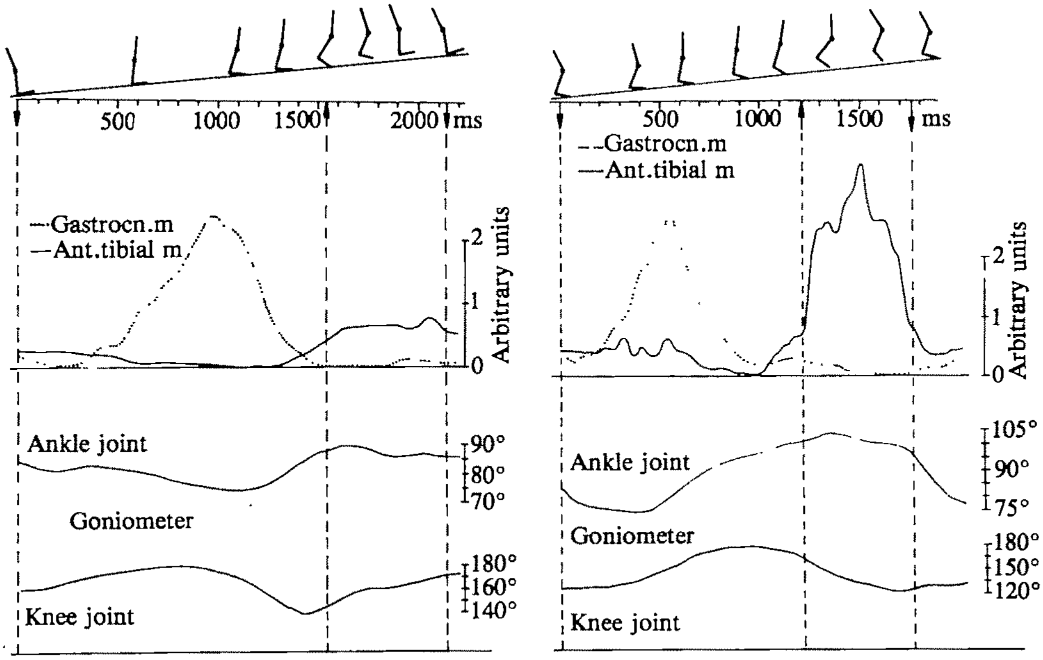

FIG. 4. Rectified and averaged (n = 30) EMG of tibialis anterior and gastrocnemius muscles together with the averaged goniometer signals of ankle and knee joint angles of a normal subject (*left side*) and a spastic patient (*right side*). Vertical lines indicate touch down (↓) and lift up (↑) of the foot. Above the time scale the leg position during the different phases of a gait cycle on the inclined (10 deg) treadmill is reconstructed from the knee and ankle joint goniometer signals. Note that in the spastic patient ground contact is made by the ball of the foot followed by an earlier dorsiflexion and a correspondingly earlier gastrocnemius activation.

subject during a slow gait on the inclined treadmill. It is obvious that the reciprocally organized pattern of muscle innervation is not altered in the spastic patient compared to the normal subject; however, the foot remains in an extended position during the swing phase despite a strong EMG burst in tibialis anterior. This result was found in all patients with spasticity. Some patients additionally showed small but characteristic differences in the timing and pattern of leg muscle activity.

In a few patients the foot was kept in such a plantar flexed position during the swing phase that the ball of the foot rather than the heel made contact with the ground at the beginning of the stance phase. The averaged EMG and goniometer records of such a patient are shown in fig. 4. Compared to the normal subject, on the left side the foot is dorsiflexed earlier at the beginning of the stance phase, indicated by the goniometer record. Correspondingly an earlier onset of gastrocnemius activity occurs which ends in the middle of the stance phase, with the beginning of foot extension. In most patients, however, the onset of gastrocnemius activity was normal. Premature gastrocnemius activity combined with an abnormally large tibialis EMG was seen in some cases, especially when the treadmill was a little inclined (10 per cent, *see* fig. 4). There were, however, no basic differences in the timing of EMG bursts in these patients when gait was compared on inclined and level ground.

In a few patients with spasticity, reciprocally organized bursts of EMG occurred in the leg muscles especially at the beginning and end of the stance phase. The frequency of this synchronized activity was in the range of 7 to 9 Hz and was not a specific observation in spastic patients. Some patients with Parkinson's disease and older normal subjects (above 60 years old) also showed a tendency to synchronized EMG bursts. Patients who showed such EMG synchronization did not show a more pronounced clonus phenomenon than other spastic patients. In all recordings which showed such an EMG synchronization, the gastrocnemius EMG bursts never occurred during the swing phase and therefore cannot explain failure of foot elevation in these patients.

Results obtained from investigation of 12 legs in 10 spastic patients are summarized in fig. 5 and compared with results obtained from normal subjects. The mean values with standard deviations show no significant differences in the strength and timing of the gastrocnemius EMG between normal subjects and patients during walking. The timing of tibialis anterior activity is not disturbed in the patients. The strength of the recorded tibialis activity, however, is significantly greater in the patients during the swing phase. In normal subjects the foot is actively dorsiflexed during swing by a tibialis anterior EMG burst of small amplitude. In patients with spastic paresis the foot dorsiflexion is lacking despite the stronger tibialis EMG. As fig. 5 demonstrates, in these patients the ankle joint remains at an angle of about 100 deg during the swing phase although the amplitude of tibialis EMG is on average more than twice as large as in normal subjects. This fact becomes more obvious when the amplitude of tibialis anterior activity during

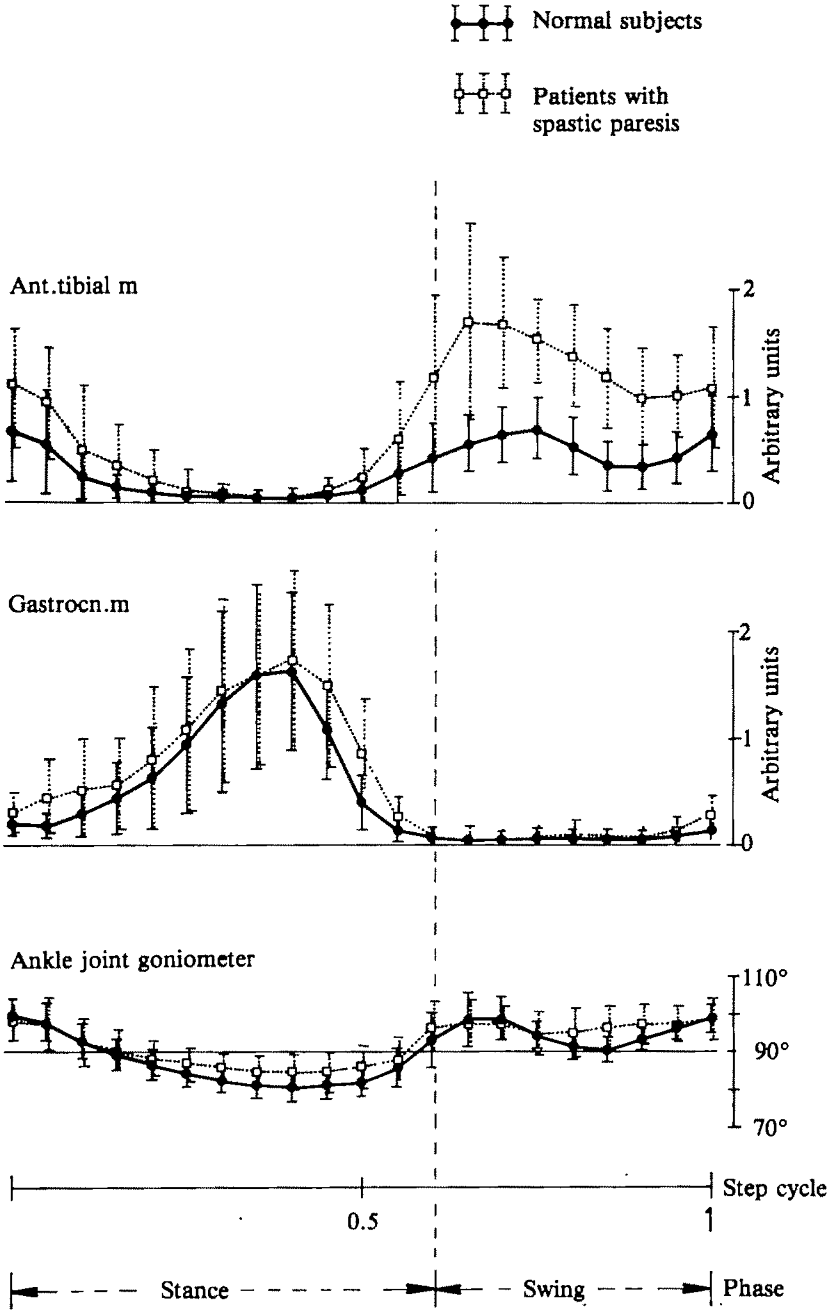

FIG. 5. Mean values with standard deviations of the rectified and averaged (n = 30) tibialis anterior and gastrocnemius EMG together with the ankle goniometer signal of a normalized step cycle obtained in 20 normal subjects (n = 24) and 10 patients with spasticity (n = 12). Vertical line as in fig. 2.

the gait is related to that reached during its maximal voluntary isometric contraction. On average the tibialis EMG in the swing phase reaches 68 per cent (±17) of the EMG of maximal isometric voluntary contraction compared to 27 per cent (±13) in the normal subjects, while the gastrocnemius activation is rather similar in respect to that of its maximal isometric voluntary contraction (patients 77 per cent ±40; normals 57 per cent ±33).

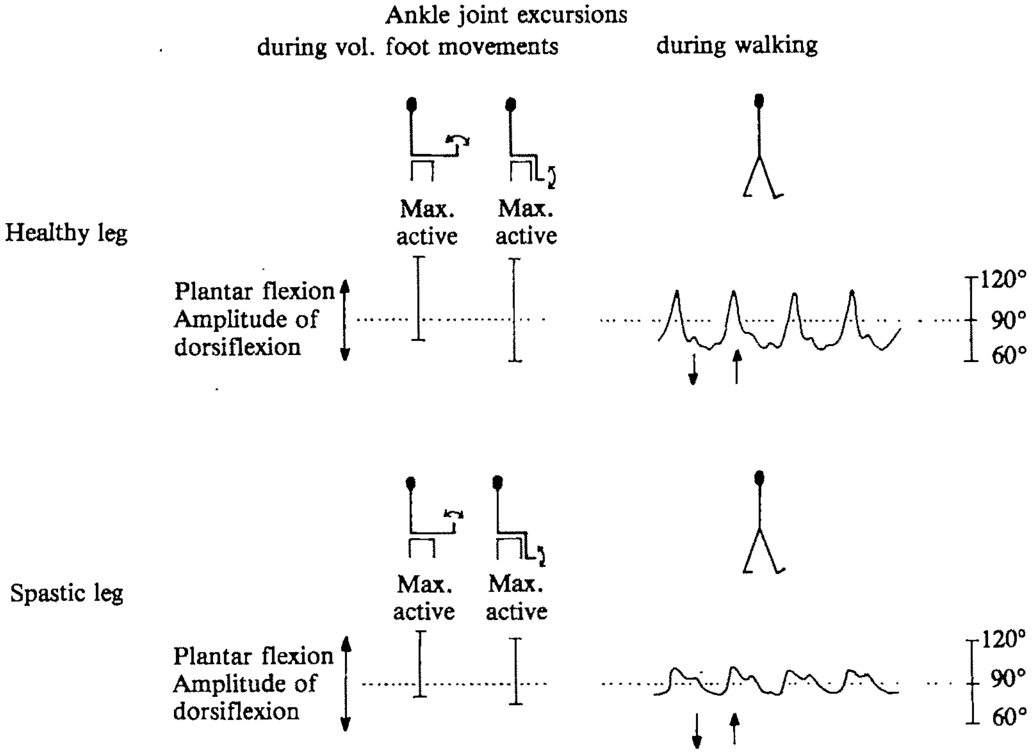

FIG. 6. Ankle joint signal of the right normal (*above*) and the left spastic leg (*below*) of a patient with a spastic hemiparesis (not listed in the Table). On the left side the angle amplitude during maximum voluntary isotonic dorsi- and plantar flexion of the foot with the outstretched and the flexed leg (knee ankle 90 deg) is shown. On the right side the ankle joint movements during the gait are shown. Arrows indicate touch down (↓) and lift up (↑) of the foot.

The differences in the changes of ankle joint angle between a normal and a spastic leg, recorded from a patient with spastic hemiparesis, are demonstrated in fig. 6. In the spastic leg the maximum amplitude of angle reached in this joint during maximum voluntary isotonic movements is not only restricted in dorsiflexion but also in plantar flexion of the foot compared to the healthy leg. In the gait the amplitude of angle ankle joint excursions is also much smaller in the spastic leg compared to the normal one. In both legs the angle amplitudes obtained during maximum voluntary plantar and dorsiflexion of the foot are not reached in the gait.

Pattern of EMG Activity Recorded in Parkinsonian Gait

In keeping with clinical observations, the length and duration of the steps of patients with Parkinson's disease were usually found to be much shorter than in normal subjects and also in spastic patients (step duration: normal subjects 1530 ms±220; spastic patients 1600 ms±280; parkinsonian patients 1270 ms±180). The relative duration of swing and stance phases within a step cycle did not differ between normal subjects and patients with Parkinson's disease: the stance phase in normals amounted to 61 per cent±3 and in both groups of patients to 62 per cent±5 of one step cycle.

Fig. 7 shows a typical recording of the gait of a parkinsonian patient. He was treated with L-dopa, benserazide and amantadine. In this patient the reciprocal leg muscle activity is preserved, and the amplitude of the EMG of tibialis anterior during the swing phase is obviously much greater than that of normals which is similar to the findings in spasticity. In contrast to the spastic patients the foot is dorsiflexed during the swing phase as in healthy subjects.

A typical example of the averaged EMGs and ankle goniometer records from a patient with Parkinson's disease is shown in fig. 8. As demonstrated in this figure, the gastrocnemius EMG amplitude during the stance phase in some of the patients was smaller than in the normals. Beside these changes in strength of recorded muscle activity it can be seen that, despite the very short step cycle, the timing of the innervation of tibialis anterior and gastrocnemius is well preserved.

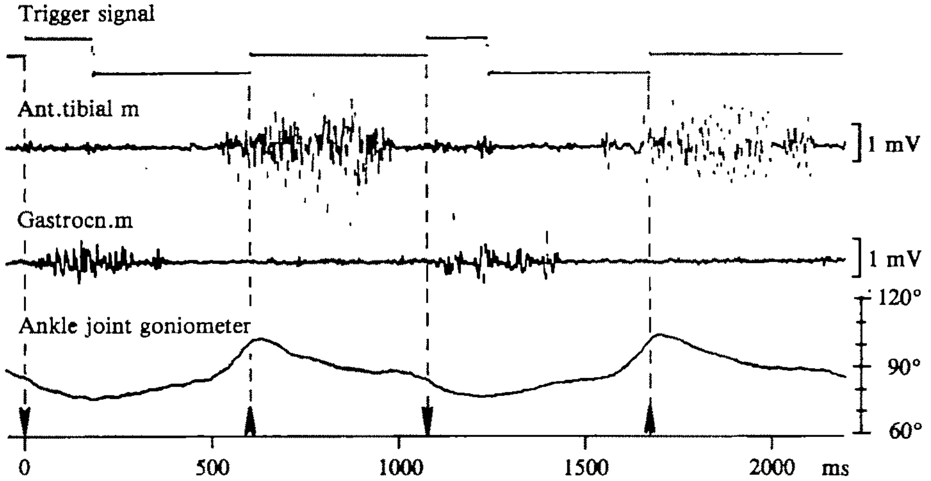

FIG. 7. Original recording of 2 step cycles during the gait of a parkinsonian patient. *From top to bottom:* signal of electrical switches (*see* fig. 1); EMG of tibialis anterior gastrocnemius muscles; and goniometer signal of ankle joint angle.

The mean values of the averaged and normalized data obtained in 10 patients (13 legs) are summarized in fig. 9 and can be compared with the values found in normal subjects. This histogram is very similar to that obtained in spastic patients with the exception of a slightly reduced gastrocnemius EMG and an active dorsiflexion of the foot in the swing phase. In some of the patients with Parkinson's

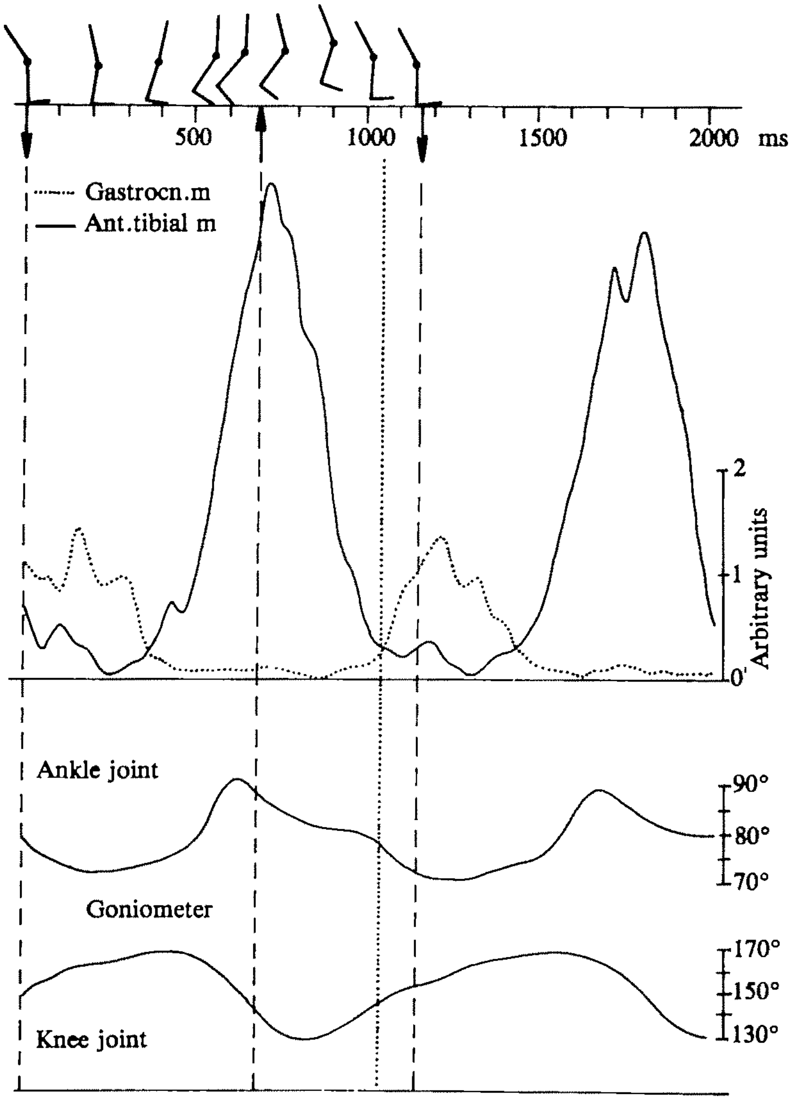

FIG. 8. Rectified and averaged (n = 30) EMG of tibialis anterior and gastrocnemius muscles triggered by heel contact together with averaged goniometer signals of ankle and knee joint angles of a patient with Parkinson's disease. Vertical lines indicate the signal released by the electrical heel contact (↓) (actual ground contact was reached a little earlier, indicated by the dotted line) and uplifting (↑) of the foot. The leg position above the time scale was reconstructed as described in fig. 4.

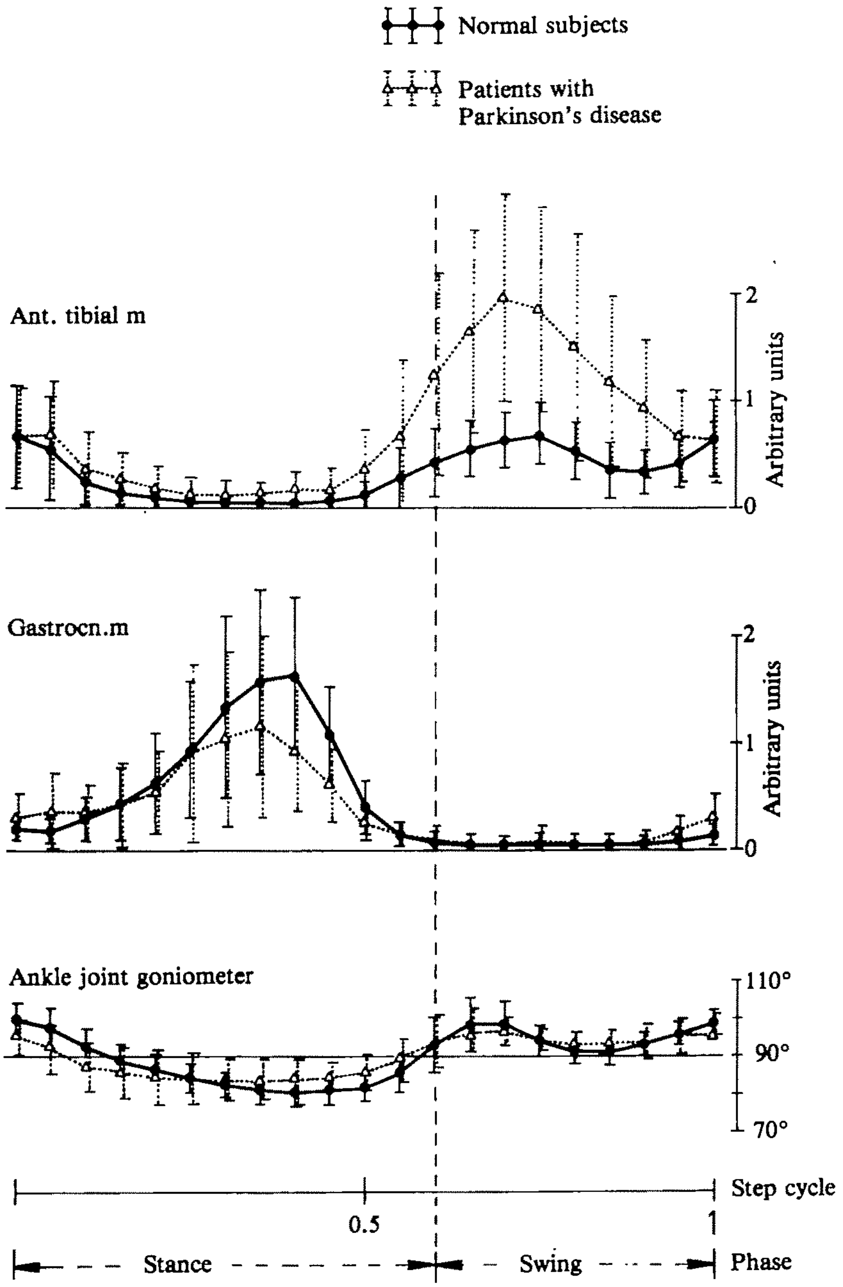

FIG. 9. Mean values with standard deviations of the rectified and averaged (n = 30) tibialis anterior and gastrocnemius EMG together with the goniometer signal of ankle joint angle in a normalized step cycle obtained in 20 normal subjects (*see* fig. 5) and 10 patients with Parkinson's disease (n = 11). Vertical line indicates the end of the stance phase.

disease the EMG activity of tibialis anterior during the gait reached the amplitude recorded during maximum voluntary isometric contraction. The tibialis EMG amplitude during the swing phase of the gait was, in relation to the maximal voluntary isometric activity, still little higher in rigidity than in spasticity (73 per cent ± 25). As in spastic patients the EMG amplitude of tibialis anterior recorded while the subject maintained an isometric tension of 5 kg was not higher in the patients than in the normals.

Influence of Temperature on Leg Muscle Innervation in Patients with Spasticity and Rigidity

It is well-known that spastic patients complain about increasing muscle stiffness when it is cold. In experiments on cats the activity of the muscle spindles when the temperature is lowered decreases (Eldred, Lindsley and Buchwald, 1960), so a reduction in muscle activity should be expected after cooling the leg. In some patients with mild spasticity of both legs we therefore repeated the recordings after surrounding one leg with a rubber bag containing hot water and the other leg with a bag containing ice for fifteen minutes and maintaining these conditions during the gait. The gait was not disturbed by these manipulations, but there were distinct changes in the innervation pattern in all the patients tested. While in the cooled leg the EMG tibialis anterior was slightly increased, especially at the start of walking, the activity of gastrocnemius was not significantly changed. However, in the warmed leg the EMG of tibialis was significantly reduced while that of gastrocnemius was not much altered (fig. 10). Such an increase of leg muscle activity on the cold and a decrease on the warm leg was observed in all 5 patients tested and also in the 2 normal subjects tested. In the patients these EMG alterations were associated with changes in angle of ankle joint during walking as can be seen in fig. 10. While the amplitude of angular movement at the ankle joint is smaller in the cold leg, it is larger in the warm leg compared to the controls at normal temperature.

DISCUSSION

It is well-known that patients with spastic paresis and with parkinsonian rigidity have difficulty in walking and one characteristic symptom is their difficulty in lifting the foot during the swing phase of locomotion. This paper describes the results of experiments designed to investigate the physiological abnormalities leading to this disability of gait in terms of changes in the EMG activity recorded from the appropriate prime movers. The most striking observation was that the increased muscle tone in patients with spasticity or rigidity cannot be explained by the electrical activity of the antagonist muscle groups of the limb. In particular there was no coactivation of tibialis anterior and triceps suræ muscles, which could be responsible for the muscle stiffness complained about by the patients. While, in spastic patients, the usual increase in activity of tibialis was not sufficient to

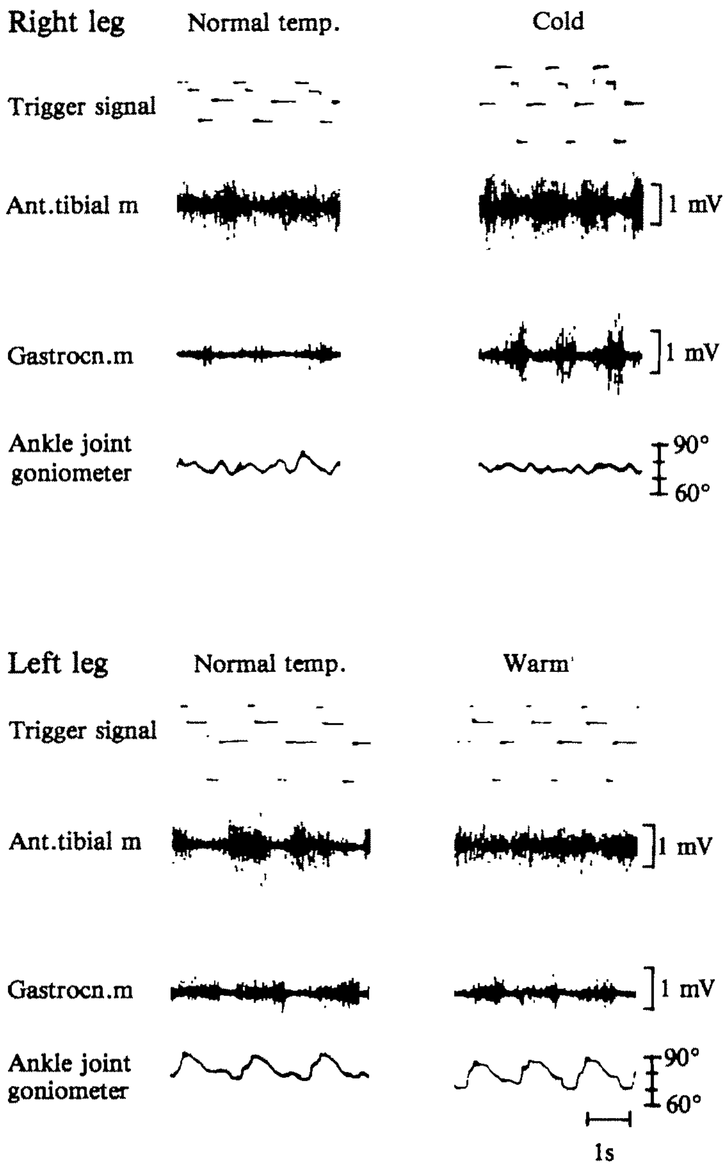

FIG. 10. Changes in the innervation pattern after warming (*below*) and cooling (*above*) the legs of a spastic paraparetic patient. *Left side:* raw EMG of mm. tibialis anterior and gastrocnemius together with trigger and goniometer signal of ankle joint angle of both spastic legs before changing the temperature. *Right side:* the same parameters after warming the left and cooling the right leg for fifteen minutes.

counteract the tension exerted by the electrically silent triceps suræ during the swing phase of the gait, the patients with Parkinson's disease were usually able to lift up the foot, with an increased tibialis EMG. In contrast to the enhanced tibialis EMG, the amplitude of the calf muscle activity in both groups of patients did not differ significantly from that obtained in normals.

These main results are probably surprising in view of the exaggerated tendon reflexes and of the findings of electrophysiological investigations made on the resting leg in spastic patients. The main pathophysiological suggestions have included facilitation of the α-motoneuron pool (Nathan, 1973; Nöel, 1973) and hyperactivity of fusimotor neurons (Rushworth, 1960; Dietrichson, 1973). However, increased muscle activity has not been reported in active movements of these patients, either in the older literature (Altenburger, 1937) or in recent investigations (Knutsson and Richards, 1979). In the latter paper very few patients showed muscle coactivation. Further, the investigations of Vallbo, Hagbarth, Torebjörk and Wallin (1979) and Hagbarth, Wallin and Löfstedt (1973) on spindle activity in rigidity and spasticity gave no indication of an excessive group Ia input due to exaggerated fusimotor drive in these patients. How can we explain these discrepancies in the light of our results?

First, the clinical and electrophysiological observations of the exaggerated reflexes in the resting leg in these patients do not necessarily imply a higher activity of motoneurons in active movements. As we know from physiological recording from group Ia afferents in the cat (Prochazka, Westerman and Ziccone, 1977) and reflex studies in man (Dietz and Noth, 1978), the gain of the spinal reflexes in active movements is enhanced by the activation of γ-motoneurons, probably from supraspinal brain centres. Therefore, the muscle activity obtained during stretches of the resting muscle is quite different from that observed during stretches in active motor tasks (Dietz and Noth, 1978).

Secondly, it is known from the experiments of Engberg and Lundberg (1969) and Grillner (1975) on decerebrate cats that the neuronal mechanisms for the regulation of simple locomotion patterns with a reciprocal muscle innervation is organized within the spinal cord. Therefore, after a lesion of the pyramidal or extrapyramidal tracts an alteration of the reciprocal innervation pattern in such stereotyped motor tasks should not be expected.

Thirdly, we do not suppose that the premature innervation of the gastrocnemius muscles during the stance phase observed in some spastic patients is due to a lowered reflex threshold as supposed by Knutsson and Richards (1979). In running, it was shown (Dietz *et al.*, 1979) that the strength of gastrocnemius activity is largely stretch-induced. Also during walking the maximum stretch of triceps suræ is connected with the peak of gastrocnemius EMG. In normal gait this falls into the second half of the stance phase. As can be seen from recordings of spastic patients (*see* fig. 4), the extended foot position causes an earlier stretching of the triceps suræ combined with a premature activation of the gastrocnemius at the beginning of the stance phase.

The pathophysiological mechanism underlying increased muscle tone and the frequent relative inability of the patients to lift up the extended foot during the swing phase remains an open question. There are theoretically three possible ways of explaining this phenomenon. First, the lack of active dorsiflexion could be explained by a mechanical obstruction at the ankle joint, although the foot is passively dorsiflexed in the stance phase of gait. The changes seen in the amplitude of ankle angle after warming or cooling the leg muscles, however, make a resistance within the ankle joint unlikely.

Secondly, it could be argued that the EMG of tibialis anterior is not as effective in force production as in normals. There is some evidence that patients with spasticity and rigidity have lower discharge rates of motor units (Dietz, Hillesheimer and Freund, 1974; Freund, Dietz, Wita and Kapp, 1973). This altered discharge behaviour could result in a lower force output because of the relatively higher proportion of unfused muscle fibre twitches within the respective muscles (Allum, Dietz and Freund, 1978). However, there were neither significant signs of paresis on clinical examination nor was there a difference between patients and normals in the EMG amplitude needed to maintain an isometric tension of 5 kg.

The remaining possibility is that the triceps muscle fibres themselves or the connective tissue within this muscle are mainly responsible for the muscle hypertonia. The changes in the innervation pattern and the length-tension behaviour of the leg muscles observed after altering the temperature surrounding the leg muscles make us suppose that the muscle fibres rather than the connective tissue are responsible for the increased muscle tone. Slow muscle fibres which show an increased resistance to stretching due to their contractile properties are known from animal experiments (Browne, 1976; Lännergren, 1967). Such a property of muscle fibres could explain some of the main observations made in the experiments described here. Indeed, histologically and histochemically distinct muscle fibre changes (atrophy of phasic motor units and hypertrophy of tonic units) were reported in these patients and were thought to be connected with the increased muscle tone in spasticity and rigidity (Edström, 1970; Tomonaga and Tanabe, 1973). There is, however, a report in which the structural muscle fibre changes observed are considered to be rather unspecific (Ahlqvist, Landin and Wroblewski, 1975). It therefore remains an open question whether the changed muscle properties are induced transsynaptically or are the consequence of spasticity or rigidity as the result of the disuse of white muscle fibres.

The results obtained in our patients must be regarded as a very small part of the complex phenomenon of spasticity and rigidity. They might lead to changes in the physiotherapy which should be prescribed for these patients. Further electrophysiological and histological studies are needed to clarify the pathological mechanism of spasticity and rigidity.

SUMMARY

The surface electromyogram (EMG) of mm. tibialis anterior and triceps suræ was recorded in 10 patients with spasticity, 10 patients with rigidity and 20 normal subjects and correlated with the changes in ankle joint angle during the different phases of the gait cycle. While the strength and timing of EMG activity recorded from triceps suræ during the stance phase of gait did not differ from that of normal subjects, the EMG of tibialis anterior was significantly stronger during the swing phase in both groups of patients. Although the reciprocally organized innervation pattern of the leg muscles was preserved, spastic patients could hardly lift up the affected foot during the swing phase despite the enhanced activity of tibialis anterior. There was no coactivation of the calf muscles during the hyperactivity of tibialis anterior. Therefore, no electrophysiological explanation could be found for the increased muscle tone in either group of patients. The possibilities of reduced force development by the muscle fibres of tibialis anterior or of some mechanical obstruction in the ankle joint were largely excluded as alternative explanations underlying the impeded elevation of the foot. We suppose that in both diseases the muscle fibres undergo changes which are responsible for increased muscle tone in spasticity and rigidity. The pathophysiological mechanism of these changes remains unknown.

ACKNOWLEDGEMENTS

We thank Dr J. Stephens for critical review of the manuscript and Drs J. Noth and R. R. Young for helpful comments on the paper. We are grateful to Mrs Römmelt for technical assistance.

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LYMPHOCYTE-MEDIATED CYTOTOXICITY AGAINST GLIOMAS

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INTRODUCTION

IN recent years evidence has accumulated from both *in vivo* and *in vitro* studies that experimental animal tumours express antigens which give rise to an immune response (Prehn and Main, 1957; Baldwin, Embleton and Robins, 1973). Human tumour studies present far more difficulty than animal systems in which artificially-induced tumours and inbred strains of animals are used. Nevertheless, it has been possible by means of *in vitro* techniques to show that human neoplasms also possess tumour-associated antigens capable of inducing in the patient either humoral or cell-mediated responses, or both types of response (Hellström, Hellström, Sjögren and Warner, 1971; Oren and Herberman, 1971; Phillips, Sujatanond, Martuza, Quindlen, Wood, Kornblith and Dohan, 1976; Embleton, 1973).

Brain tumours have attracted less attention than other human neoplasms, partly because of the widely held view that the brain is an immunologically privileged site (Medawar, 1948), and that primary brain tumours are therefore unlikely to give rise to an immune response. Experimental studies, however, have shown that immunological rejection does occur in the brain but more slowly than at other sites (Ridley and Cavanagh, 1969). Several workers have also found that human gliomas may show lymphocytic infiltration, suggesting the existence of some type of immunological response to the tumour (Ridley and Cavanagh, 1971; Takeuchi and Barnard, 1976; Brooks, Markesbury, Gupta and Roszman, 1978). The purpose of the present study is to explore this possibility by examining lymphocytes from patients with gliomas for evidence of cell-mediated cytotoxicity against glioma cells. Ideally, lymphocytes from glioma tissue should be studied for evidence of cytotoxicity. However, this would require more tissue than is usually obtained at biopsy, and would also necessitate storage of lymphocytes in order to carry out autologous studies. It was decided, therefore, to investigate the problem by studying the effect of peripheral blood lymphocytes from glioma patients on cells of their own tumour obtained at biopsy and grown in culture. In the present study lymphocyte microcytotoxicity has been used, employing the technique described by Baldwin and his co-workers (Baldwin *et al.*, 1973). In all experiments in the present study, autologous lymphocytes were used as effector cells against tumour cells in the first *in vitro* passage. In each experiment, lymphocytes from a non-tumour control were also set up against tumour cells. In addition some patients' lymphocytes were tested against heterologous glioma cells and fœtal brain cells.

MATERIALS AND METHODS

Tumour Tissue

Tumour tissue was obtained at operation from 10 males and 11 females. Two of the males were children and all the others were adults. In some of the adult cases, a specimen of normal brain tissue was also taken and cultured.

Tissue Culture of Tumour and Fœtal Material

Fresh tumour biopsy material was transferred to Hank's balanced salt solution (BSS) containing high concentrations of antibiotics (penicillin 500 units/ml, streptomycin 500 μg/ml, gentamicin 200 μg/ml, amphotericin B 2.5 μg/ml) left as 37° C for twenty minutes, then transferred to fresh BSS and chopped finely with scalpel blades into fragments less than 1 mm^3 and left for a further thirty minutes at 37° C in BSS. Some of the fragments were transferred to tissue culture flasks (Nunc, 25 cm^2) as explants, and others were disaggregated mechanically by drawing up and down in a syringe. The suspension was allowed to settle and the supernatant removed and centrifuged. The resulting pellet was resuspended in tissue culture medium (Hank's minimal essential medium with L-glutamine, supplemented with 10 per cent fœtal calf serum, essential and non-essential amino acids with 50 units/ml penicillin and 50 μg/ml streptomycin and a carbonate/bicarbonate buffering system). Tumour cells were counted using phase-microscopy and a minimum of 1×10^6 cells placed in a 25 cm^2 culture flask, gassed with CO_2 to a pH of approximately 7.2 and incubated at 37° C. If the culture was successful, cells had usually begun to settle and spread within forty-eight hours.

Human fœtal tissue was derived from early second trimester fœtuses. Culture methods used were the same as those described for glioma culture. At the first passage, fœtal glial cells and skin fibroblasts were frozen in Hank's minimal essential medium with 20 per cent fœtal calf serum and 10 per cent dimethylsulphoxide, and stored in liquid nitrogen. Aliquots were then thawed and cultured as required.

Separation of Peripheral Blood Lymphocytes

Lymphocytes were obtained from tumour patients and control subjects. The latter consisted of healthy donors and patients with non-neurological disease. Glioma patients were matched with controls of the same age and sex.

A modification of the technique described by Böyum (1968) for separation of blood leucocytes was employed using serum-free and streptomycin-free medium throughout. Whole blood (10 to 12 ml) was defibrinated, and medium (0.25 × volume of the blood) was added to improve separation before placing on a Ficoll-Triosil gradient. Cells obtained from the gradient were washed twice in medium, counted in a hæmocytometer chamber using phase contrast microscopy and the cell concentration adjusted to approximately 1×10^6/ml. The suspension was then placed on a nylon wool column (Leukopac, Baxter Laboratories, Thetford) previously soaked in medium and pre-incubated at 37° C for thirty minutes, and non-adherent cells eluted using pre-warmed medium. Eluted lymphocytes were washed, recounted and adjusted to the required concentration. Lymphocyte viability was normally in excess of 85 per cent and only rarely was there any contamination with monocytes.

Microcytotoxicity Test

This was performed in a microtitre system in a similar way to the test described previously for animal tumours (Rainbird and Ridley, 1977). When sufficient tumour cells had grown, they were lightly trypsinized and transferred to microtitre plate wells. After twenty-four hours the plates were examined and the cells in the wells counted with a Wild M40 inverted microscope incorporating a graticule. If more than 50 cells per well were seen to be spreading, then lymphocytes prepared as described above were added to the wells at the required ratio (*see* Tables 2–5) and the plates incubated for one hour at 37° C on a rocking platform. Replicates of 4 and 8 wells were used for each combination of tumour cells and lymphocytes. Twenty μl of fœtal calf serum was then added to each well and incubation continued for a further forty-eight hours at 37° C in a moist atmosphere containing 5 per cent CO_2. At the end of this period, the supernatants were removed and the plates washed with warm buffered saline. Cells remaining in the wells were fixed in absolute alcohol for five minutes, stained with May-Grunwald-Giemsa stain, dried in a warm air oven for one hour, and counted using a stereoscopic microscope (Olympus). The percentage reduction of tumour cells was calculated using the formula:

$$100 - \frac{\text{residual cells in wells treated with test lymphocytes}}{\text{residual cells in wells treated with control lymphocytes}} \times 100$$

A positive value in the Tables indicates a cytotoxic effect, that is, fewer residual cells after treatment with test lymphocytes than control lymphocytes. The procedures used in this study were approved by the Ethics Committee of the London Hospital.

RESULTS

Details of tumour source and grade, lymphocyte source and cells against which lymphocytes were tested is given in Table 1 together with experimental numbers.

Autologous Cytotoxicity

Lymphocytes from 20 patients were tested against autologous tumour cells at various ratios of lymphocytes to target cells (Table 2). A typical result is shown in Table 3. Twelve of the patients tested had lymphocytes which were cytotoxic at one ratio or more. Percentage reduction by test lymphocytes, when compared to control lymphocytes, varied overall from 75 per cent to -26 per cent (in the latter case corresponding to a growth stimulation effect in the test wells). In those experiments in which the reduction was statistically significant ($P < 0.05$), inhibition ranged from 20 to 76 per cent; in the others, the reductions were in the range of 33 per cent to -26 per cent. Occasionally, an experiment would yield scattered results with a high average inhibition, yet would not achieve statistical significance. Such effects may reflect a highly heterogeneous cell population, differences in cell plating efficiency, or artefacts of experimental manipulation.

Cross-reactivity with Heterologous Tumour Cells (*Table 4*)

Lymphocytes from 10 patients were tested against glioma cells from other glioma patients. Four of the 10 patients showed significant cross-reaction with heterologous tumour cells.

Cross-reactivity with Fœtal Cells (*Table 5*)

Lymphocytotoxicity was noted in 5 of 11 patients tested against fœtal brain cells but no cytotoxic effect was observed in 4 other patients whose lymphocytes were tested against fœtal fibroblasts.

Relationship of Lymphocytotoxicity to Lymphocytic Infiltration and Tumour Grade

In view of previous reports of lymphocyte infiltration in gliomas (Ridley and Cavanagh, 1971; Takeuchi and Barnard, 1976; Brooks *et al.*, 1978) we decided to see whether lymphocyte infiltration correlated with lymphocytotoxicity in the present series of gliomas (figs. 1–4).

Of the 20 patients whose tumours were used for cytotoxicity, 17 were suitable for histological study. They were scored on the basis of lymphocytes per highpower field in areas remote from necrotic tissue. Our impression was that there was a correlation between lymphocytic infiltration and cytotoxicity, but on statistical analysis this proved not to be so (*P*:0.2, Fisher's exact test).

[*Text continued on page 459.*]

TABLE 1. SUMMARY OF EXPERIMENTAL MATERIAL

		No. of experiment		
Glioma specimen	*Grade**	*Autologous*	*Heterologous†*	*Fœtal brain† cells*
G5	(2)		21 (G27)	33** (G28)
G10	(2)	1		35 (G29)‡
G14	(4)	2		37 (G31)
G16	(3)	3		38 (G37)
G17	(Gliosarcoma)	4		39 (G38)
G25	(3)	5		40 (G39)
G26	(4)	6		41 (G44)
G27	(2)	7		42 (G45)
G28	(2)	8	22 (G29) 23 (G30)‡	43 (G48)
G31	(3)	9		44 (G49)
G37	(2)	10		45 (G51)
G38	(3)	11	25 (G39)	
G39	(4)	12	24 (G38) 26 (G40)	
G40	(3)	13		
G43	(3)	14		
G44	(4)	15	28 (G45)	
G45	(4)	16	27 (G44)	
G48	(4)	17	29 (G5)	
G49	(4)	18	30 (G52)	
G51	(4)	19		
G52	(Microglioma)	20		

* Kernohan, Mabon, Svien and Adson (1949). † Lymphocyte donor in brackets. ‡ G29 and G30 were not used in autologous experiments, but only as lymphocyte donors on heterologous tumour cells and fœtal brain. ** Experiments 31, 32, 34 and 36 using fœtal fibroblasts as target cells were negative and have been omitted.

TABLE 2. SUMMARY OF DATA FROM 20 GLIOMA PATIENTS (EXPERIMENTAL NUMBERS 1–20) IN WHOM CYTOTOXICITY OF PATIENTS' LYMPHOCYTES WAS TESTED AGAINST THEIR OWN TUMOUR CELLS

Cell ratio	*No. of experiment*	*Percentage cytotoxicity mean (range)*	P*
50:1	11, 12, 13, 18	14 (5 to 23)	NS
100:1	5, 16	38 (29 to 47)	< 0.01
	1, 7, 8, 10, 11, 12, 13 14, 15, 18, 19, 20	9 (−14 to 33)	NS
200:1	16	76 (42 to 76)	< 0.01
	1, 3, 4, 12, 15, 18, 20	34 (20 to 61)	< 0.05
	5, 8, 10, 11, 13, 14, 17, 19	1 (−26 to 19)	NS
400:1	16, 18	67 (60 to 75)	< 0.01
	2	28	< 0.05
	6, 9, 14, 15, 17, 19, 20	−2 (−23 to 28)	NS
800:1	9, 19, 20	37 (36 to 38)	0.05
	6	−2	NS

* Determined using the Mann-Whitney U test (Siegel 1956). Significant cytotoxicity ($P < 0.05$) was observed in experiments 1, 2, 3, 4, 5, 9, 12, 15, 16, 18, 19 and 20.

TABLE 3. TYPICAL RESULTS OF A CYTOTOXICITY TEST IN WHICH A PATIENT'S LYMPHOCYTES WERE TESTED AGAINST AUTOLOGOUS TUMOUR CELLS

		Residual tumour cells in wells			
Experiment	*Ratio lymphocytes: tumour cells*	*Patients' lymphocytes*	*Control lymphocytes*	*Cytotoxicity %*	*P value*
15	400:1	42 ± 6*	58 ± 11	28	NS
	200:1	35 ± 6	90 ± 6	61	0.014
	100:1	81 ± 25	86 ± 13	6	NS

* Results are expressed as mean ± SD and are in this experiment based on quadruplicate observations. Significance of the difference between patients and control lymphocytes were tested using the Mann-Whitney U test.

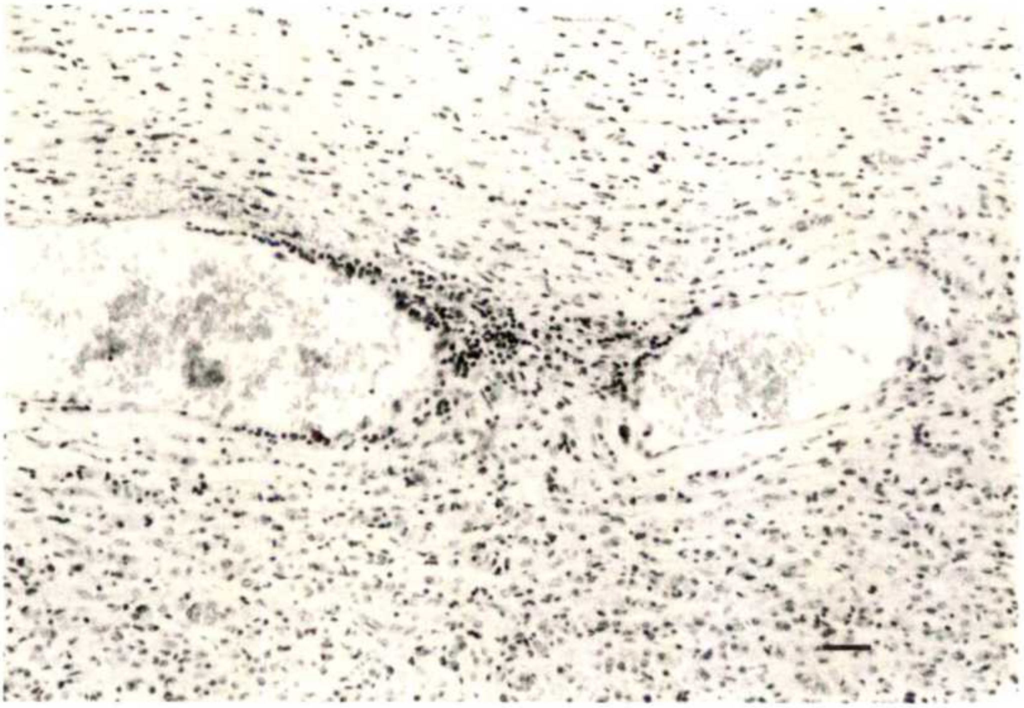

FIG. 1. Perivascular cuffing of obliquely sectioned vessel at edge of tumour. Tumour tissue (bottom of photograph) also lightly infiltrated with lymphocytes. H and E. Bar = 18 μm.

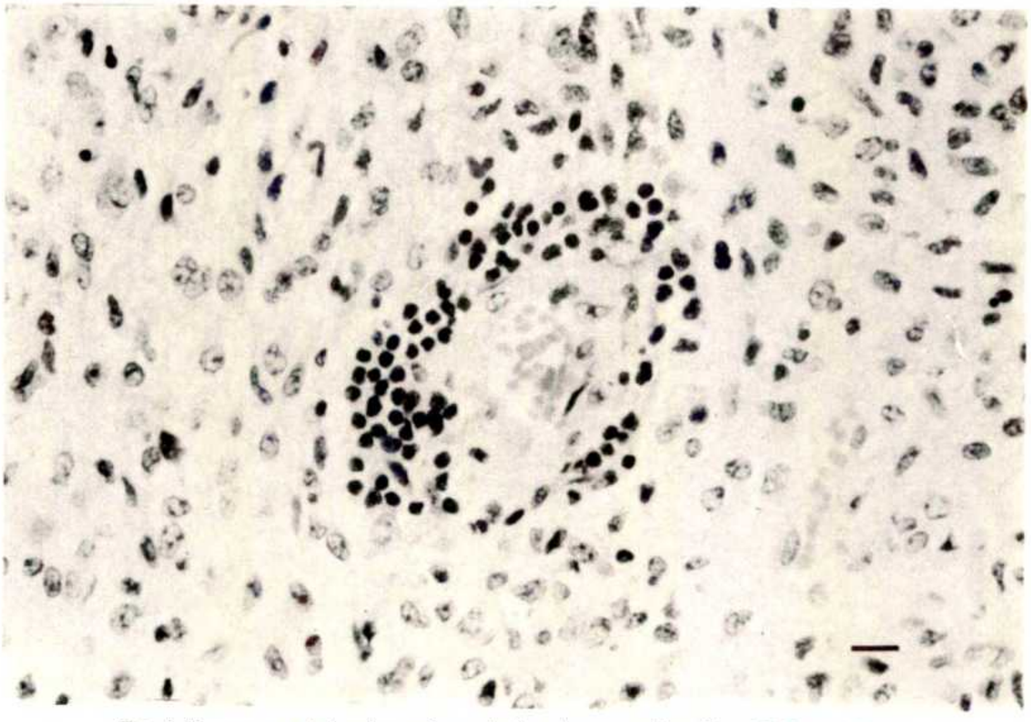

FIG. 2. Tumour vessel showing perivascular lymphocyte cuffing. H and E. Bar = 54 μm.

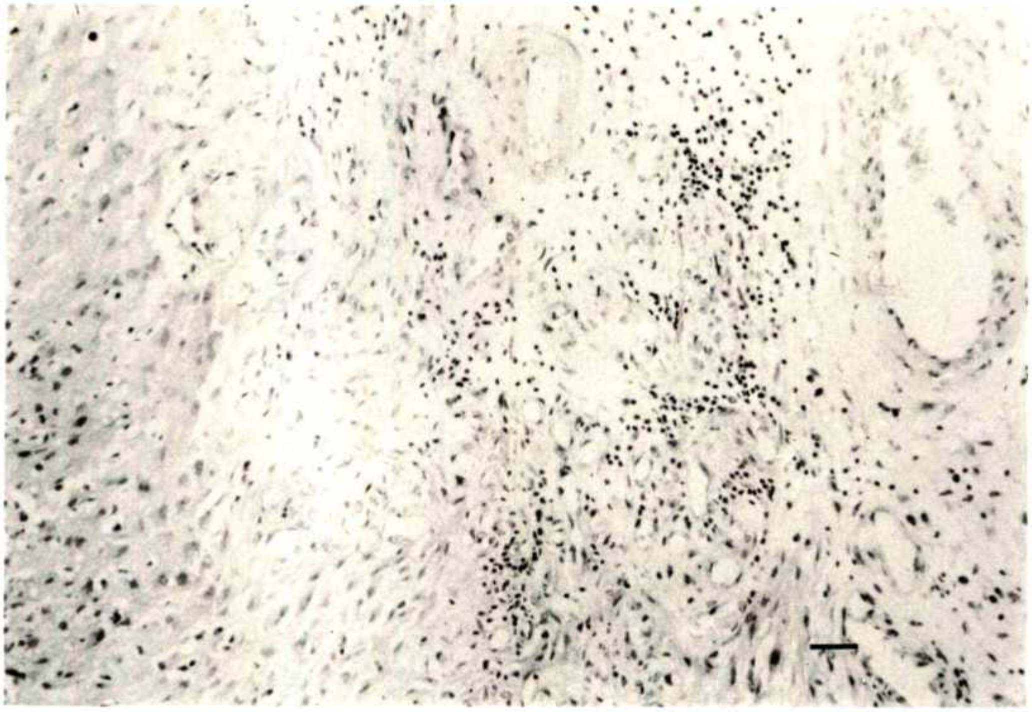

FIG. 3. Diffuse lymphocyte infiltration (*right*) at periphery of tumour (*left*). H and E. Bar = 18 μm.

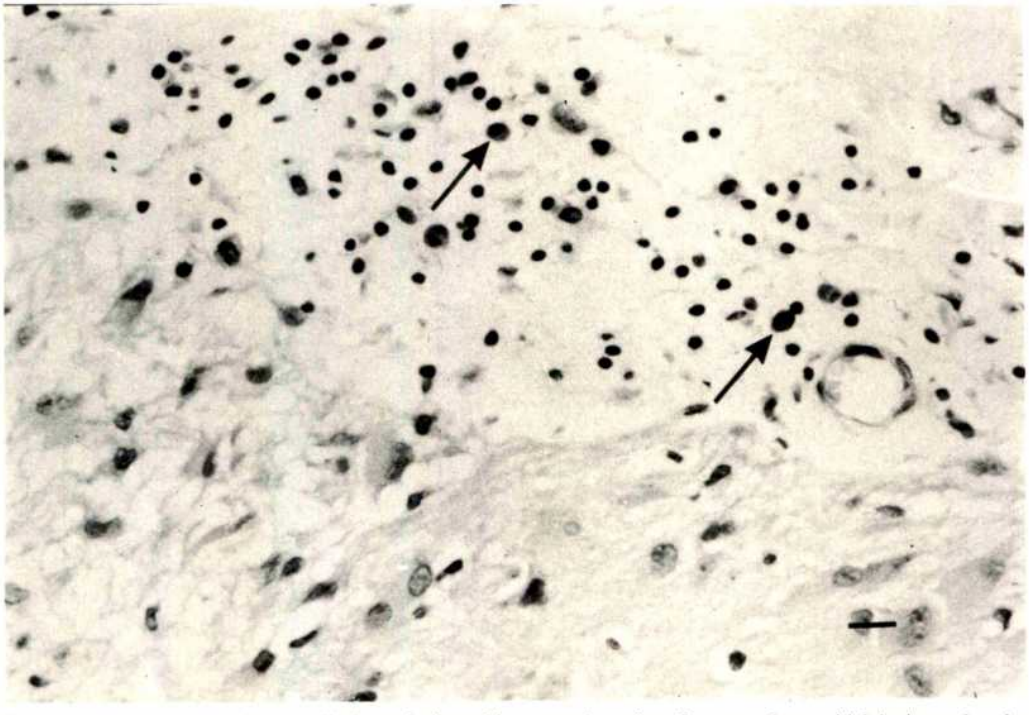

FIG. 4. Lymphocytes and plasma cells (latter indicated by arrows) at edge of tumour tissue which is situated at the bottom of the photograph. H and E. Bar = 54 μm.

Table 4. Summary of Data from 10 Glioma Patients (Experimental Nos. 21–30) in Whom Patients' Lymphocytes were Tested Against Heterologous Tumour Cells

Cell ratio	*No. of experiment*	*Percentage cytotoxicity mean (range)*	*P value*
50:1	27	30	< 0.01
	28	36	< 0.05
	25	5	NS
100:1	27	70	< 0.001
	28	66	< 0.05
	21, 23, 24, 25, 29, 30	−17 (−29 to −6)	NS
200:1	22	36	< 0.001
	27, 28	53 (37 to 69)	> 0.05
	21, 23, 24, 28, 29, 30	1 (−8 to 12)	NS
	25	−39	< 0.05*
400:1	22, 24	24 (13 to 35)	< 0.05
	21, 26, 29, 30	0 (−9 to 38)	NS

* Indicates significant enhancement of tumour cell growth in wells treated with patients' lymphocytes when compared to wells treated with control lymphocytes. Significant cytotoxicity ($P < 0.05$) was observed in experiments 22, 24, 27 and 28.

Table 5. Summary of Data from 11 Glioma Patients (Experimental Nos. 33, 35, 37 to 45) in Whom Cytotoxicity of Patients' Lymphocytes was Tested Against Fœtal Brain Cells*

Cell ratio	*No. of experiment*	*Percentage cytotoxicity mean (range)*	*P value*
50:1	38, 43, 44	3 (−11 to 11)	NS
100:1	42	52	< 0.01
	33, 37, 41	48 (33 to 82)	< 0.05
	35, 37, 38, 39, 40, 43, 45	7 (−19 to 12)	NS
200:1	41, 42, 44	70 (33 to 83)	< 0.01
	33	33	< 0.05
	35, 37, 38, 39, 40, 43, 45	7 (−19 to 12)	NS
400:1	42, 44	76 (57 to 95)	< 0.01
	37	32	NS
	45	−40	< 0.05†

* In experiments 31, 32, 34 and 36 fœtal fibroblasts were used as target cells. No significant response was observed. † Significant stimulation of target cell growth by lymphocytes were observed in this experiment. Significant cytotoxicity ($P < 0.05$) was observed in experiments 33, 37, 41, 42 and 44.

We also compared lymphocytotoxicity with tumour grade. Cytotoxicity appeared to occur more often in the more malignant tumours (6 out of 8 Grade 4 tumours, 3 out of 6 Grade 3 tumours and 1 out of 4 Grade 2 tumours) but this was not statistically significant (P:0.27, Fisher's exact test). However, if this trend were maintained in a larger sample (30 to 35) the 0.05 level of statistical significance would be achieved.

DISCUSSION

Cell-mediated cytotoxicity of glioma target cells by both autologous and heterologous lymphocytes has been reported by other authors (Levy, Mahaley and Day, 1972; Kumar and Taylor, 1973). Levy and co-workers found that the patients' lymphocytes exerted a glioma-specific effect and did not inhibit the growth of normal glia. Kumar and Taylor were able to demonstrate inhibition of glioma cell growth by heterologous lymphocytes from patients with histologically similar tumours. Wahlström and colleagues, on the other hand, considered that the cell-mediated cytotoxicity which they found in glioma patients was probably directed against glia-specific antigenic determinants rather than tumour cell antigens (Wahlström, Saksela and Troupp, 1973).

The results of the present study confirm that *in vitro* cell-mediated cytotoxicity can be demonstrated in glioma patients. Twelve out of the 20 glioma patients tested had lymphocytes which were capable of significantly reducing the number of their own tumour cells (self-reactors). Four of the 12 patients were also tested against glioma cells from other patients and 2 of them reacted against these cells. Inhibition of heterologous glioma cells was also observed in 2 other cases—one from the group of 8 patients whose lymphocytes did not show cytotoxicity against their own glioma cells, and an additional one whose cells could not be tested against her own tumour cells for technical reasons. Six of the 12 self-reactor patients were also tested against fœtal brain cells, and 4 inhibited these cells. Five of the 8 non-self-reactors were also tested against fœtal brain cells. One of these, a child with a juvenile astrocytoma, was positive and the remainder were negative.

Before discussing the possible immunological implications of the present study, two technical aspects of *in vitro* cell-mediated cytotoxicity should be mentioned. The first of these is the effect of the ratio of lymphocytes to tumour cells in the wells, and the second is the possible inhibitory effect which lymphocytes from non-tumour-bearing individuals may exert on tumour cell growth. In all experiments we used several ratios of lymphocytes to tumour cells and found that of the 12 patients with lymphocytes capable of reducing the number of tumour cells, 8 did so at a ratio of 200:1 which seemed to be the optimal ratio for our system. However, we also found that as the ratio of lymphocytes to target cells increased, the number of target cells in both test and control wells diminished in some experiments, whereas in others the number of target cells increased. The fact that control as well as test lymphocytes showed these effects suggests that they are not immunological in nature. It may be that the reduction in target cell numbers with high ratios of lymphocytes was due to an exhaustion of metabolites in the medium, while the increase in target cell numbers may be due to trephocytic (feeding) effects by the lymphocytes as discussed by Fidler (1973).

Some authors have reported that lymphocytes from non-tumour patients and healthy donors may inhibit the growth of non-brain tumours (Takasugi, Mickey and Terasaki, 1973; Kay and Sinkovics, 1974). These workers, however, compared untreated wells (containing tumour cells only), with wells containing both tumour cells and lymphocytes. This results in anything up to a fifty-fold increase in cell numbers in the test wells compared to the control wells. With such differences in the number of cells per well, physiological effects are important and may account for the apparent inhibition of tumour cell growth by non-tumour patients' lymphocytes. We considered that it was better to compare wells containing similar numbers of cells, so our results are based on a comparison of test and control lymphocyte wells containing comparable numbers of cells.

The mechanism of target cell inhibition has not been specifically investigated in the present study, but two major mechanisms have been proposed. These are cytotoxicity, which involves killing of tumour cells by lymphocytes (reviewed by Cerottini and Brunner, 1974), and cytostasis (Jamieson and Wallace, 1970) in which it is proposed that lymphocytes inhibit the growth of the tumour cells without actually destroying them. In our system cell killing appeared to be more important than cytostasis. Thus in experiments where the supernatant was collected at the end of the incubation period and examined microscopically, large pleomorphic cells which appeared to be dead tumour cells were observed as well as lymphocytes. These cells took up trypan blue and on further incubation of pooled supernatants no growth of tumour cells was seen. These observations do not preclude the possibility that a growth inhibitory mechanism may be operating concurrently, but favour cell death as the more important mechanism.

In 4 out of 10 patients tested, cross-reactivity of patients' lymphocytes against other tumours of similar histological type was observed (Table 4). These results and those of Kumar and Taylor (1973) indicate that lymphocytes from glioma patients may react against heterologous glioma cells. Evidence from other authors using serological methods (Wahlström, Linder, Saksela and Westermark, 1974; Coakham and Lakshmi, 1975) supports the hypothesis that some gliomas share common surface determinants, and Coakham and Lakshmi have suggested that this could indicate a viral ætiology of gliomas. Evidence favouring such an ætiology has been obtained by Cuatico, Cho and Spiegelman (1976). In a study of 31 human gliomas and 11 meningiomas, evidence of a nucleic acid sequence consistent with a virus particle was found in 25 of the gliomas and 3 of the meningiomas. However, this type of study does not necessarily mean that a virus is the cause of the tumour, since it could simply be an opportunistic virus or indeed a common nucleic acid constituent of appropriate size and structure. On the other hand, Bigner and his collaborators have succeeded in inducing gliomas in dogs and inbred rats by intracerebral injection of the Schmidt-Ruppin strain of Rous sarcoma virus, suggesting that some gliomas may be virus-induced (Bigner, Odom, Mahaley and Day, 1969; Wilfgong, Bigner and Self, 1973).

Lymphocytes from 11 patients were tested for reactivity against fœtal brain cells (Table 5). Five (3 males and 2 females) were found to have lymphocytes which exerted significant cytotoxicity. Of these 5 patients, 4 (G31, G44, G45 and G49), were amongst the self-reactor group, which showed cytotoxicity against their own tumour cells, and one (G28) was from the non-self-reactor group (*see* Tables 1 and 2). One of the 5 patients was pregnant when she first presented with neurological symptoms, and another was multiparous. We are therefore unable to exclude the possibility that sensitization to fœtal antigens may have occurred independently of the presence of a glioma. Nevertheless, the occurrence of such reactivity in 3 males does raise the question of the presence in some gliomas of a fœtal de-repressed antigen or perhaps of an antigen which is only found on dividing cells.

The lack of correlation between cytotoxicity and lymphocytic infiltration is not altogether surprising, first, because the numbers examined were small, and secondly the lymphocyte populations which infiltrate tumours may not be identical with those that mediate cytotoxicity *in vitro*. However, the findings of Brooks and colleagues (1978) may also be relevant. These workers found that patients whose gliomas showed perivascular lymphocytic cuffing survived longer than those in whom there was only diffuse lymphocytic infiltration. Unfortunately, perivascular cuffing was present in only 3 of the 17 gliomas we examined, compared to 67 of 149 cases in Brooks's study. Since the proportion of highly malignant gliomas (those in which lymphocytic infiltration is usually most marked) was the same in both studies, the low proportion of perivascular cuffing in our series may reflect a bias induced by selection only of those tumours which grew in culture. Whatever the explanation, 2 of the 3 patients in our series who showed perivascular cuffing (G16 and G39) gave a positive lymphocytoxic result and the other (G49) was negative. We cannot, on the basis of such a small number of cases, offer any comment on Brooks's findings, but clearly the association between perivascular cuffing and patient survival merits further study.

The final point remaining for consideration is whether the lymphocyte-mediated response detected in 12 out of the 20 patients is directed against a glioma-specific tumour antigen or a glioma-inducing virus, or whether it is simply a side effect due to an immunological reaction against antigens released from glial cells damaged as a result of tumour growth. Levy and co-workers (1972) were able to grow normal glial cells from tumour patients, and using these cells as targets, found that tumour patients' lymphocytes which killed glioma cells did not affect the patients' own normal glial cells, that is, lymphocytotoxicity was tumour-specific. We were unable to substantiate Levy's observation because not all our normal brain cultures grew from material obtained at operations, and in those that did, we could not exclude the possibility that the specimen of 'normal brain' may have contained tumour cells. In any case, using normal adult glial cells as target cells probably only allows lymphocytes to react with surface glial antigens, and does not rule out the possibility that in glioma patients it may be the liberation of intracellular antigens from damaged glial cells which sensitizes the lymphocytes. Thus several glial-specific proteins, such as S100 and glial fibrillary acidic protein, have been isolated from normal glial cells (Dittman, Axelson, Norgaard-Pederson and Bock, 1977) and these or similar proteins could act as sensitizing agents. It is also worth noting in this connection that Wahlström has reported that a soluble extract of brain tissue from a victim of a road traffic accident induced blast transformation of lymphocytes from 9 of 14 glioma patients but had no effect on normal lymphocutes (Wahlström, 1973). The latter finding suggests that lymphocyte sensitization to glial antigens can occur in glioma patients. One way round the problem of whether the immune response demonstrable *in vitro* is directed against tumour or glial antigens would be to examine lymphocytotoxicity in a series of non-tumour patients who have sustained brain damage as a result of trauma or ischæmia. If such a study showed lymphocytotoxicity it would suggest that the latter is directed against glial cell components rather than a tumour antigen. For the present, however, this remains an open question.

SUMMARY

The effects of peripheral blood lymphocytes from patients with glioma on glioma cells grown in culture was studied using an *in vitro* microcytotoxicity test.

Lymphocytes from 12 of the 20 patients studied showed significant cytotoxic activity against their own tumour cells. Four of them reacted against heterologous glioma cells and 4 also showed some reactivity against fœtal brain cells.

An attempt to correlate *in vitro* cytotoxicity with the degree of lymphocytic infiltration of the tumour suggested an association, but the number of cases examined was too small to achieve statistical significance.

ACKNOWLEDGEMENTS

The study was initially supported by a grant from the Medical Research Council and subsequently by a locally organized Clinical Research Grant from the North East Thames Regional Health Authority. We thank Mr T. King, Professor E. S. Watkins and Mr D. Hardy for providing the glioma biopsy material, and Dr K. Scholtz for assistance in grading the gliomas and assessing the degree of lymphocytic infiltration in the tumours.

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(*Received November 13, 1980*)

Brain, (1981), **104**, 465–491

GATING OF SOMATOSENSORY EVOKED POTENTIALS DURING DIFFERENT KINDS OF MOVEMENT IN MAN

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INTRODUCTION

THE central nervous system disregards as irrelevant much of the afferent information gathered by the sense organs. This selectivity is generally termed attention, and has the property that attention can be directed towards any desired part of a wide range of available sense data.

There seems to be in addition a somewhat more automatic form of selection of afferent information, comprising the interruption or attenuation of the flow of sense data because some action being performed renders it irrelevant or misleading. One instance of this is the momentary interruption of the transmission of visual signals at the lateral geniculate body during a saccadic eye movement (Adey and Noda, 1973). Such interruption is often termed gating.

Just as the flow of visual sense data is momentarily interrupted while the eye is redirected, so it might be that some classes of somatic sensory analysis could be interrupted during movement, in order to prevent confusion.

Again, afferent information used in the control of movement might be selectively gated during a movement, in a way that depends on the nature of the movement. A fraction of the afferent activity that is relevant to the reflex control of one part of a movement might be irrelevant to another; and if reflex regulation plays a part in the control of segments of movement, then gating of the afferent limb of such reflexes could be part of the means by which movement control is effected. It would be expected that this kind of afferent gating during movements would be particularly important during learned, skilled, movements. If some phases of a skilled movement are to be reflexly assisted by afferent information that is gated out for other phases, then that gating would be likely to be applied at suprasegmental levels, since there is little evidence that the spinal cord is capable of learning of the degree of complexity required.

Skilled sensory gating of this sort could provide one of the reasons for the transcortical routing of some automatic reflex responses first suggested by Phillips

(1969). One of the advantages of such routing (rather than dealing with the reflex response at segmental level) would be that reflexes could be selected, modified and gated in a much more subtle way if they are transcortical than if they are spinal. There is now accumulating evidence that some automatic (probably transcortical) long-latency responses do serve complex functions, such as the maintenance of posture (Marsden, Merton and Morton, 1978) or support (Marsden, Rothwell and Traub, 1979).

There is also evidence that intact cutaneous and joint sensation from a moving part is important in some circumstances in sustaining long-latency stretch reflexes relating to movement of that part (Marsden *et al.*, 1977).

Good evidence is available to show that gating of somatic sensory information can occur during movement. In the awake cat, evoked potentials recorded at the medial lemniscus in response to radial nerve stimulation are slightly reduced during movement of the limb (Ghez and Pisa, 1972; Coulter, 1974); the gating here presumably is occurring at dorsal column nuclear level. This observation does not of course answer the question whether gating is also occurring at a cortical level. Papakostopoulos, Cooper and Crow (1975), recording from implanted cortical electrodes in man, showed a reduction of the cerebral evoked responses to stimulation of the median nerve when a movement of the index finger was being performed, in comparison with the resting condition. This reduction occurred particularly in the postcentral region, whereas the response in the precentral region was largely maintained. The suppression of the early components of the somatosensory evoked potential (SEP) found by Papakostopoulos *et al.* was in agreement with the findings of some earlier workers (Giblin, 1964; Broughton, Regis and Gastaut, 1965; Coquery, Coulmance and Leon, 1972). Lee and White (1974), however, had found only some enhancement of a late component of the SEP during movement, an effect which they regarded as non-specific. Hazemann, Audin and Lille (1975) found that SEP suppression preceded and accompanied movement of the stimulated hand.

The next thing we need to know is how this gating action is controlled, and what parameters of the movements are important. Control could be exerted from above: for example, suppression of some afferent signals could be carried out by discharge corollary to the output of the motor system. Alternatively, control could be exerted from the periphery; one kind of afferent activity could gate another. Again, a gating signal whatever its source could exert its action at various levels on the ascending pathway.

It is possible to devise relatively simple experiments that distinguish between these possibilities; and which, in the 'peripheral' case, give some information as to the class of afferent activity that is responsible for the gating action. As well as investigating these questions, we attempted to determine the extent to which the gating action is 'focused' to control the afferent activity from the moving part, without altering afferent transmission from adjacent non-moving parts. Some such experiments have been briefly reported by us (Craggs, Rothwell and Rushton, 1979).

METHODS

Tasks

Controlled flexion movements of the distal phalanx of the thumb or finger were performed against a lever connected to a servo-controlled printed motor (Marsden *et al.*, 1976). There were four alternative tasks:

(1) holding the lever against a constant force ('hold');
(2) moving the lever at a constant velocity against a constant force ('track'). Standard movement 20 deg in 1 s;
(3) no force or movement ('do nothing');
(4) passive flexion of the digit at constant velocity by the motor, to whose lever the digit is taped ('passive').

Movement of the lever was linked with the horizontal movement of a vertical line on an oscilloscope face in front of the subject. When holding, the subject attempted to keep the line stationary in the centre of the screen. When tracking, another line was provided which moved spontaneously at a steady speed across the screen, and the subject was required to keep the two lines one above the other as nearly as possible. A fixation spot was also provided at the centre of the screen, and the subject was instructed not to follow the moving lines with his eyes. Observations were made on eight normal subjects, of ages ranging between 24 and 53 years. Observations were made on 8 normal subjects, of ages ranging between 24 and 53 years whose results form the body of the paper, and on 6 patients with Parkinson's disease and thalamotomy whose results are reported briefly towards the end of the paper.

Stimulation

A single 0.2 ms shock for each trial was applied through a pair of wire ring electrodes around the proximal phalanx, to stimulate the digital nerves of the right thumb. The stimulus was set at about 3 × threshold so that the sensation was strong but not painful (voltage 60 to 90). For the 'hold' and 'do nothing' conditions the stimulus occurred every 4 ± 1.5 s. For the 'track' and 'passive track' conditions the stimulus occurred within ± 0.15 s of the moment when the tracking digit passed through 10 deg flexion.

In some of the experiments we ensured that the nerve was similarly strongly stimulated in all the task conditions by recording the median electroneurogram at the wrist. In other experiments we recorded the result of graded strengths of stimulation.

Recording

Silver-silver chloride scalp electrodes in the region of the somatosensory arm area were used, with linked mastoid reference electrodes. An optimum electrode placement was found for each subject by initially attaching 4 electrodes in a square of side 5 cm, the most anterior and medial being at 10/20 position C3. Following a trial run, the electrode which gave the largest primary response in the SEP was selected and a symmetrically contralateral electrode was attached. The same electrode position was used in any subsequent experiments employing that subject. The subject was seated in a comfortable chair with a headrest, in order to minimize the possibility of head movement artefact. The shock was not strong enough to make the subject jump.

The scalp EEG was initially amplified using Devices 3160 preamplifiers (0.16 Hz to 2.5 kHz, 10 μV/cm) and then averaged using a DEC PDP 12 computer. A 250 ms sweep time was used (1 point/ms), with the stimulus occurring after the first 50 ms. Three further channels were used, one to record a 50 ms, 10 μV calibration pulse, one to record the thumb position, and one the electromyogram from flexor pollicis longus.

Sixty-four sweeps were averaged for each run. Three runs were generally done for each task condition in an experiment. The runs for the different task conditions were interlaced, against the possibility that progressive change in the size or form of the SEP might occur during the course of an experiment.

Measurement

The form of the evoked potential was as given for example in fig. 1. The various components are there termed according to the polarity-latency convention. Our latencies are actually about 5 ms longer than the names imply, because our stimulation site is more distal than the conventional one.

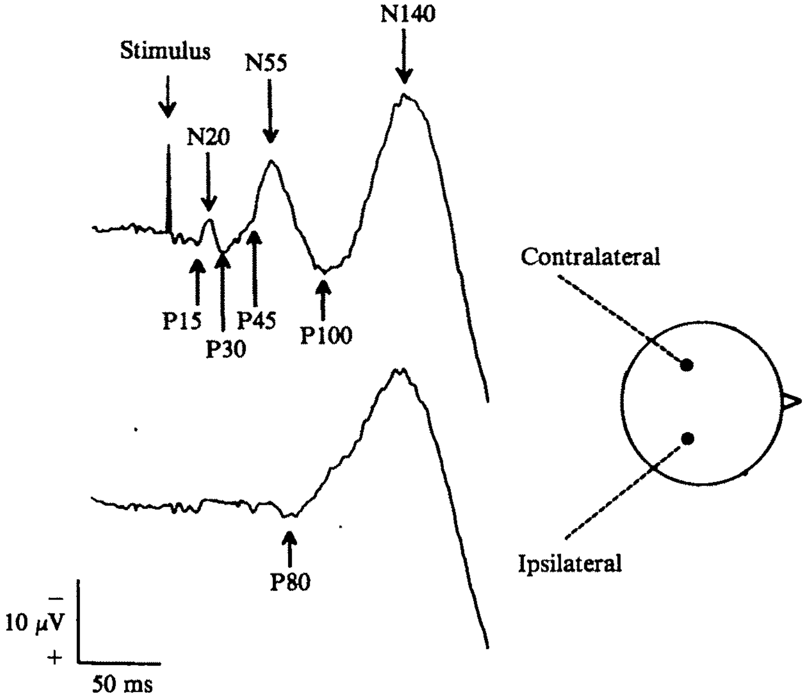

FIG. 1. SEP components following a single shock to the right thumb (200 μs, 60 V) given 50 ms after the start of the 256 ms recording sweep. Monopolar recordings, conventional polarity-latency notation. Average of 192 (3 × 64) trials. N20-P30 termed 'primary complex'. P45-N55 termed 'secondary complex'. Subject D.R.

When we introduced the different tasks (*see* fig. 4) it was clear that some components are task-sensitive and others much less so. We were anxious to quantify these changes in a meaningful way, and felt that the method used should as far as possible separate the contribution of different generators. There is no general convention as to whether base-peak or peak-peak measurement should be used (Donchin, Callaway, Cooper, Desmedt, Goff, Hillyard and Sutton, 1977), but peak-peak amplitude measurements are easier to make, and would be appropriate where the adjacent peaks selected derive from the same cortical generator. This implies that whatever montage is used, the two peaks should always maintain opposite polarities.

It is well established that P15 (the earliest component resolved using our system with a 250 ms sweep) is subcortical in origin (Cracco, 1972) as are other small waves that occur at latencies between 15 and 18 ms (King and Green, 1979; Abbruzzese, Favale, Leandri and Ratto, 1978). It is also established that the N20 and P30 components of the N20-P30 'primary complex' (Goff, Matsumiya, Allison and Goff, 1977; Abbruzzese *et al.*, 1978) arise from similar cortical sites in the contralateral somatosensory area, and they are presumed to arise from the same generator. P25 when present is believed (Goff *et al.*, 1977) to be derived from a different generator.

Of the later waves, P45 and N55 also arise in the contralateral somatosensory area (Goff *et al.*, 1977). P30 and P45 can usually be separately identified, with a plateau between them, in our records, although occasionally the plateau is so far from level that one or other of the positive peaks is hard to identify. P80 is larger ipsilaterally in our records, while P100 is contralateral (in both cases in agreement with the findings of Goff *et al.* (1977)). N140, the negative component of the vertex potential, is again well-known to be derived from a different generator from P100. So P100 is hard to measure meaningfully, since it is surrounded by unrelated peaks. Also, according to Goff *et al.* (1977), P100 is partly myogenic, although this applies mainly to the part of it that is best recorded in the frontal region.

It seems then that there are two biphasic complexes derived from the contralateral sensorimotor cortex, and these are the N20-P30 'primary complex' and P45-N55, which might be termed the 'secondary complex'.

In order to interpret the meaning of the behaviour of these two complexes under the different task conditions, it is also necessary first to establish whether they arise from identical or from slightly different cortical sites. This is dealt with below under the heading 'Localization of responses'. Secondly, we need to establish whether the 'secondary complex' arises as a later stage of processing of afferent activity previously expressed in the 'primary complex'; or whether it reflects the late arrival at the cortical level of signals in slow afferent fibres. This is dealt with below under the heading 'Effect of graded strengths of stimulation'. We do not intend to suggest any analogy between our 'secondary complex' and the 'secondary response' described in the deeply anæsthetized cat by Forbes and Morison (1939) and further analysed by Dempsey, Morison and Morison (1941).

RESULTS

Localization of Responses

In order to establish whether the N20-P30 ('primary') and the P45-N55 ('secondary') complexes arise from different foci, we arranged a cruciate array of electrodes anteposteriorly and mediolaterally, intersecting at the standard electrode site, usually C3 (fig. 2). We recorded evoked potentials from this array set up as bipolar chains (fig. 2A) and monopolarly using the usual reference site (fig. 2B). The right of fig. 2 shows the apparent sources of the generators of the primary and secondary complexes, derived (2*a*) by phase reversal and (2*b*) by amplitude maximum. It is seen that the secondary complex is localized about 2 cm anterior to the primary, and that the two methods of localization agree closely.

Effect of Graded Strengths of Stimulation

It is generally assumed that the P45-N55 wave reflects a later stage of processing of the same afferent volley than that responsible for N20-P30. It is important for our purpose to establish whether this is actually the case, or whether the P45-N55 secondary complex might (in whole or part) signal the late arrival of a volley for example along Group III afferents. Dawson (1950) gave results which suggested that the two complexes grew concurrently when he used graded electrical stimulation, and that they were therefore not derived from different fibre populations; but that was done before he had invented response averaging. More recent investigators of the SEP response to graded stimulation have been mainly interested in the relation between sensory magnitude and the amplitude of one or other component of the EP (reviewed by Regan, 1972), rather than in the sources of the various components. There is, however, evidence that in patients with spinothalamic lesions (as judged clinically), the SEP is often normal, while in patients with dorsal column lesions (as judged clinically) the SEP is grossly abnormal or absent (Halliday and Wakefield, 1963). The different components of the SEP were not there separately analysed.

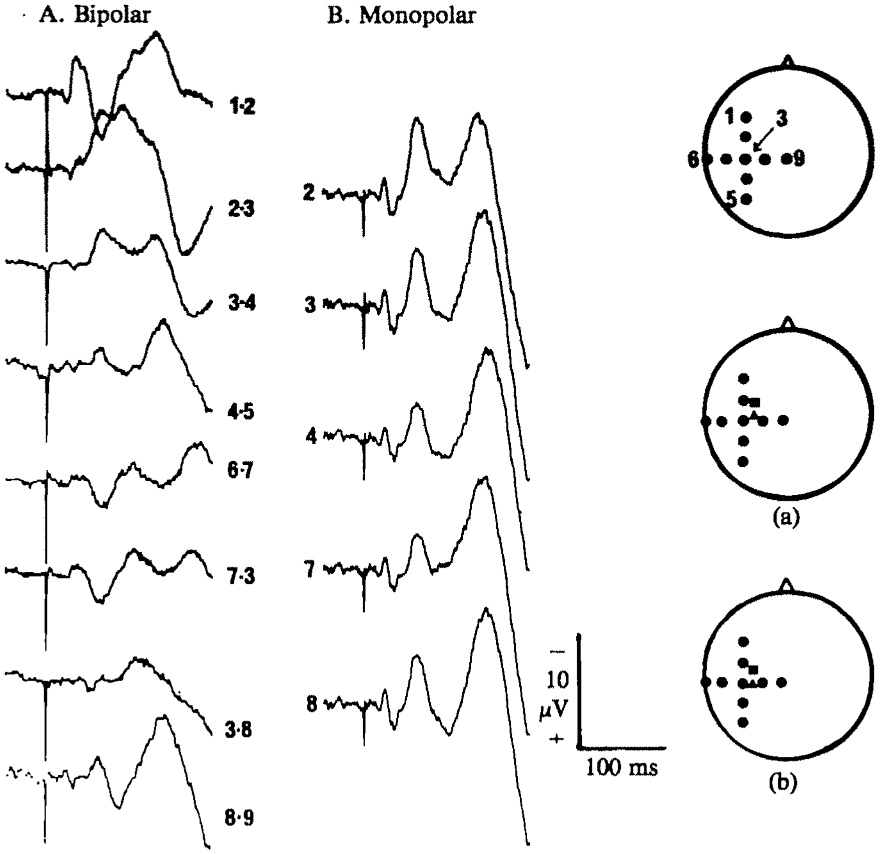

FIG. 2. Localization of primary and secondary complexes using bipolar (A) and monopolar (B) montages. *Top right*, electrode numbering: 2, 4, 7 and 8 are omitted for clarity. Spacing 2.5 cm. *Middle right*, (a) localization of primary complex (▲) and secondary complex (■) using bipolar montage. *Lower right*, (b) localization of primary complex (▲) and secondary complex (■) using monopolar montage.

One-hundred and ninety-two trials under each of the four conditions; different conditions intercalated in blocks of 64. Subject D.R. ▲ = N20-P30. ■ = P45-N55.

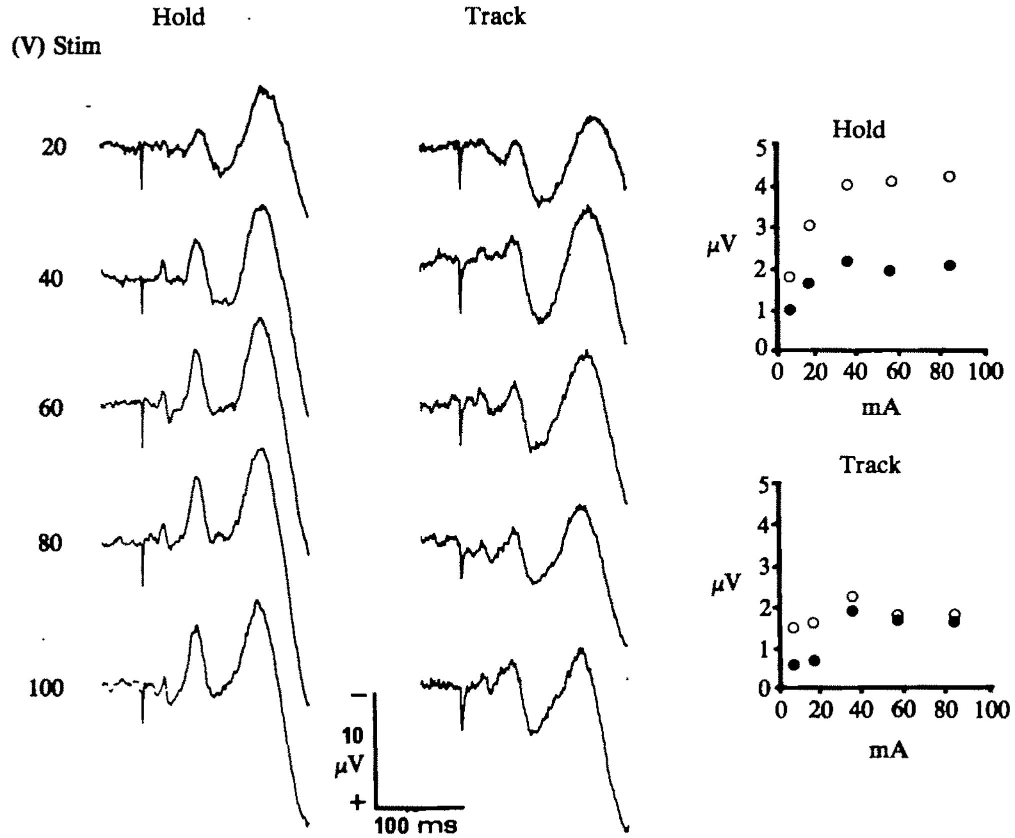

FIG. 3. Effect of graded strength of stimulation on primary complex (●) and secondary complex (○) in 'hold' (*left and upper right*) and 'track' (*centre and lower right*) conditions; 20, 40, 60, 80 and 100 V settings corresponded to 7, 17, 35, 57 and 85 mA pulse currents, respectively. Intercalated blocks of 64 trials, 3 blocks for each condition. Subject D.R.

We therefore recorded the SEP in response to various stimulation pulse currents. Fig. 3 shows the response to graded stimulation while the subject was performing the 'hold' and 'track' tasks. The lowest stimulation pulse current (7 mA) was just above threshold for radiation of the stimulus sensation into the thumb. Stimulation at the two highest levels (57 and 85 mA) was judged painful, while stimulation at the lower levels was judged painless. Both the primary N20-P30 and the secondary P45-N55 complexes continue to increase in size up to a pulse current of 35 mA but not beyond, suggesting that indeed these two waves are caused by activity in the same afferent fibre group. The lack of significant change in any of the EP components over the range where stimulation becomes painful makes it seem unlikely that Group III afferents contribute significantly to them.

Effect of Varying the Nature of the Task

The four standard tasks are described under Methods. A representative example of the form of response obtained in a typical experiment is shown in fig. 4. Each response shown is the average of 192 trials. It is clear from inspection of these results that the secondary complex is markedly suppressed under the conditions that involve movement ('track' and 'passive') in comparison with those conditions that involve no movement ('hold' and 'do nothing') while the primary complex is much less affected by the nature of the task. Passive movement is almost as effective in suppressing the secondary complex as is active movement, in this subject (as in 7 of the 8 normal subjects). (In one well-practised subject (D.R.) passive movement, initially effective, became less and less effective at causing secondary complex suppression: the effect of active movements was maintained).

The result was quite contrary to our initial expectation, which was that a 'gating' action might result in the responses being different during an active task ('hold' or 'track') from the response obtained when the subject was not active ('do-nothing' and 'passive track'). However, it was a result that was obtained consistently, and was clearly seen in the results for each of the normal subjects.

Fig. 5 gives a grand-average of the responses, all experiments up to May 1979 under the standard conditions on the right thumb being included (31 runs in 7 subjects) together with the calculated ±SEM.

When a paired t-test is applied considering the five main component amplitudes separately and comparing them between the four conditions for each subject the results are as shown in Table 1. The size of the secondary complex (P45/N55) is greatly reduced for the 'track' condition when compared with the 'hold' condition (8.3 μV to 3.6 μV). The same applies when the 'passive track' condition is compared with 'do nothing' 8.88 μV to 3.8 μV). The size of the primary response is reduced much less (1.5 μV to 1.1 μV) by active movement, but this suppression is just significant ($P < 0.05$). The small reduction of the primary response by passive movement is statistically insignificant (1.6 μV to 1.3 μV).

Figs. 4, 5 and Table 1 tell us that when the shocked digit is moving (whether that movement is active or passive) the resulting SEP is altered when compared

TABLE 1. MEAN ± SEM OF SEP AMPLITUDE IN 8 SUBJECTS, MANY OBSERVED MORE THAN ONCE. EACH EXPERIMENT COMPRISES 192 SWEEPS

	Hold $n = 41$	*Track* $n = 31$	*Do nothing* $n = 21$	*Passive* $n = 19$
Baseline N20	1.55±0.16	1.11±0.15*	1.59±0.24	1.26±0.14
N20-P30/45	4.61±0.26	3.04±0.27***	4.41±0.39	3.46±0.29
P30/45-N55	8.35±0.39	3.57±0.35***	8.88±0.61	3.80±0.38***
N55-P80	9.33±0.62	7.48±0.69*	9.41±0.97	6.27±0.64
P80-N140	14.47±0.90	11.33±0.91*	11.75±1.37	11.76±1.08

For each component, the 'hold' and 'track' conditions are compared (unpaired 2-tail t-test) and the significance of any difference is shown to the right of the track column. 'Do nothing' and 'passive' are similarly compared. * = $P < 0.05$. *** = $P < 0.001$.

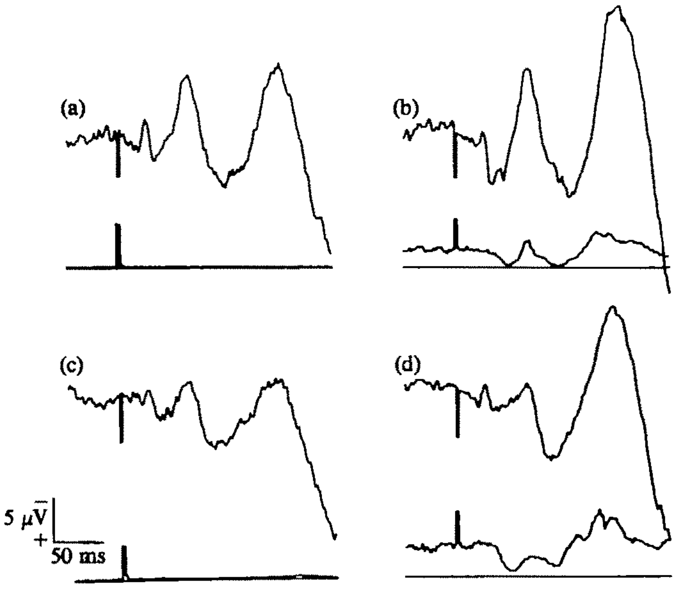

FIG. 4. Effect of varying task on SEP. Average of 192 trials. (a) 'do nothing', (b) 'hold' 0.08 Nm torque, (c) passive track 20 deg/s, (d) 'track' 20 deg/s, 0.08 Nm torque. Rectified averaged surface EMG from flexor pollicis longus is shown below each trace, with its zero baseline. Calibration 5 μV for SEPs, 50 μV for REMGs. Intercalated blocks of 64 trials, 3 blocks for each condition. Subject N.D.

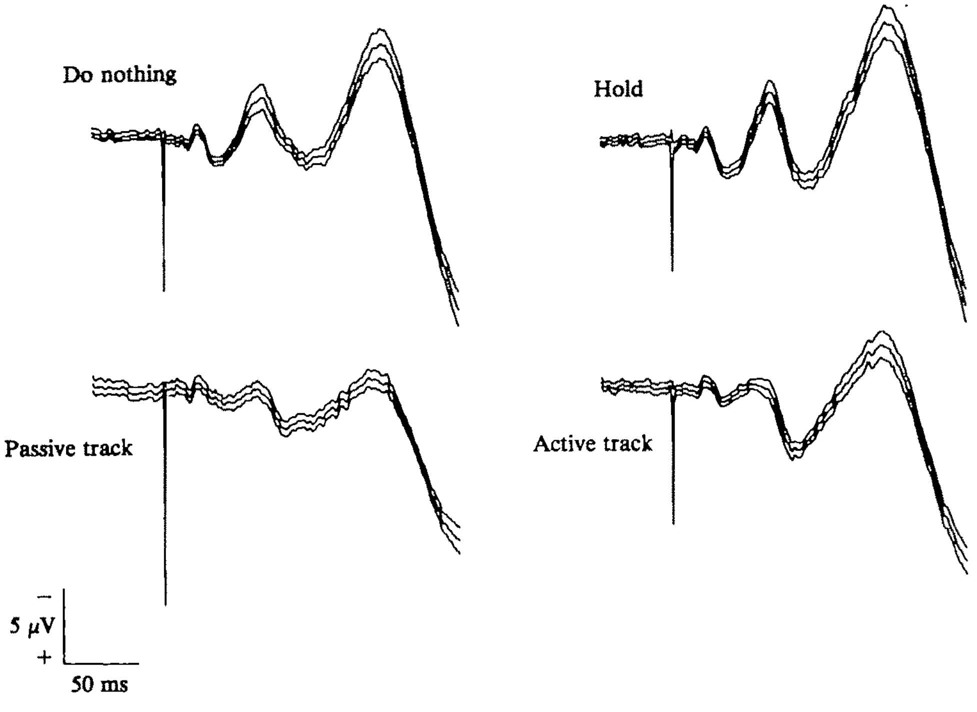

FIG. 5. Grand average of SEPs of seven normal subjects (31 runs in each condition) ± SEM for the same four conditions as fig. 4.

with that obtained when the digit is stationary (whether it is then active or resting).

We therefore needed to exclude the possibility that the shock might be less effective while the digit is moving, perhaps through a change in the relationship of stimulating electrode and digital nerve, or through a change in the effectiveness of skin contact. This we did by recording the right median compound electroneurogram at the wrist during the various tasks. Fig. 6 shows the result of such an experiment, indicating that the effectiveness of the nerve stimulation was not significantly different in the various conditions.

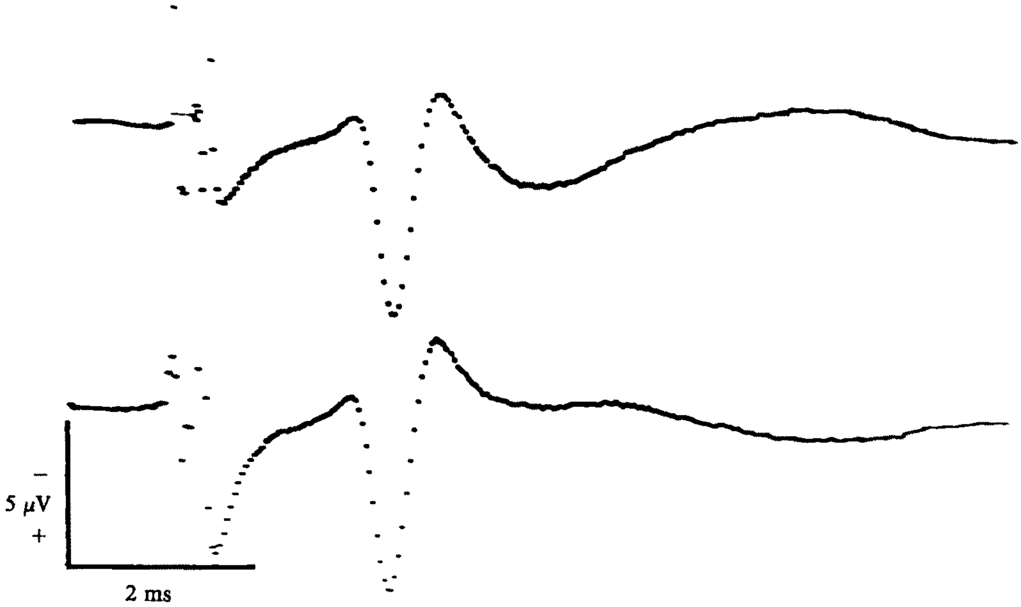

FIG. 6. Varying task has no effect on right median electroneurogram, 10 ms sweep, 192 trials. Subject J.R. *Upper trace*, 'track' conditions. *Lower trace*, 'hold' conditions. Calibration 5 μV, 2 ms.

Since passive as well as active movement is effective in gating the secondary complex, it appears that some part of the afferent activity that accompanies an active or passive movement (and is absent when the digit is stationary) is crucial in controlling the processing of the SEP. In order to decide what class of afferent information this is, it would be helpful to know at what velocity the gating becomes effective, and how the gating effect varies with changes in velocity and force.

Effect of Varying the Velocity of Movement

Fig. 7 (right) shows the SEP associated with the 'hold' task and with three different velocities of tracking. The velocities used are shown in the figure; the fastest was judged to be nearly as fast as a controlled tracking movement could easily be made in the circumstances of the experiment. Force was kept constant in these experiments. Between 0 and 20 deg/s, increasing velocity was associated

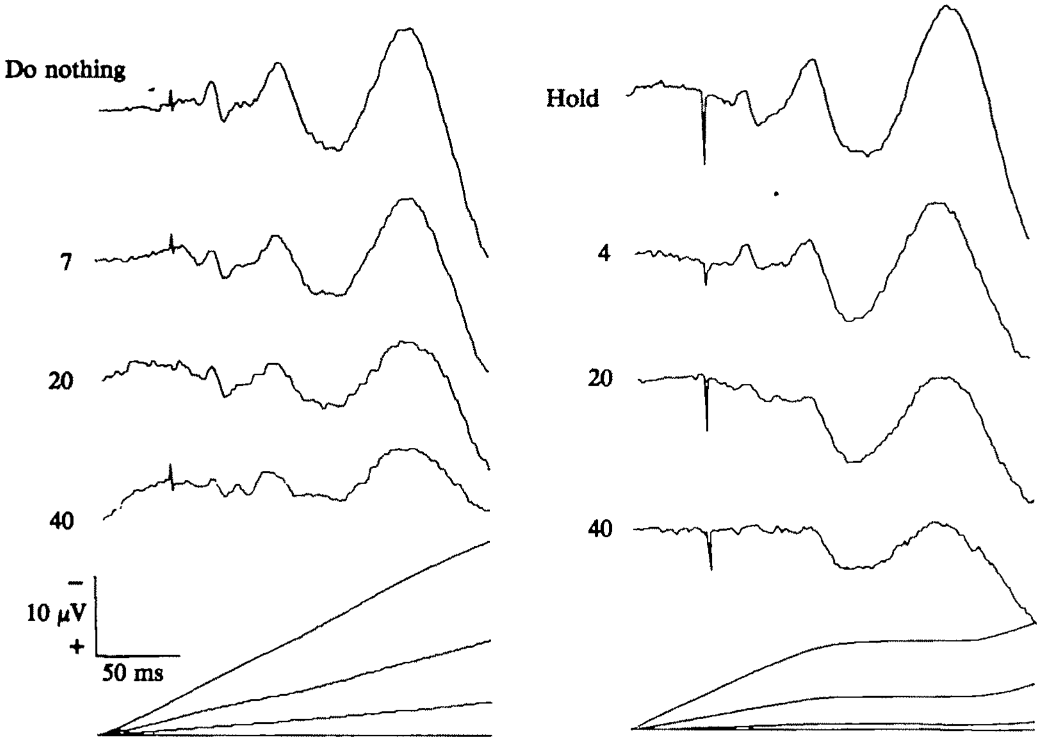

FIG. 7. Effect of varying velocity of movement. *Upper part*, SEPs, 'do nothing', 7, 20, 40: signify increasing velocity of passive movement (0, 7, 20 and 40 deg/s). 'Hold', 4, 20, 40: signify increasing velocity of active movement (0, 4, 20 and 40 deg/s). *Lower part*, position traces. Passive movements (*left*) are servo-controlled. Active movements (*right*) are perturbed by the reflex responses to the digital nerve stimulus. Intercalated blocks of 64 trials, 3 blocks for each condition. Subject D.R.

with increasing suppression (Table 2). 40 deg/s was not significantly different in its effect from 20 deg/s.

The relevant afferent pathways then are velocity-sensitive and capable of distinguishing, for example, between 10/s and 20/s flexion velocity. The secondary complex begins to be suppressed at the lowest velocity, while at the higher velocity the relatively insensitive primary complex and late vertex wave come to be suppressed as well.

Fig. 7 (left) also shows the results for a similar experiment but with the different movement velocities carried out passively. Zero velocity is then the 'do nothing' condition.

Effect of Varying Force

For the active task, we can explore the effect of varying the load. Fig. 8 shows the result for each of three load conditions for 'hold' and 'track' tasks. It seems clear that over this four-fold range of load, load is not a controlling variable.

Effect of Varying the Active Digit

In all the experiments considered so far, the digital nerves of the right thumb were stimulated and the right thumb was performing the task. In order to determine how closely focused is the task-related SEP suppression the same tasks were performed by various other digits, while always stimulating the digital nerves of the right thumb.

Fig. 9 illustrates the results of such an experiment. Fig. 9a, b, c give the responses with the usual arrangement (right thumb both performing and stimulated) for the 'hold', 'track' and 'passive' tasks. In fig. 9d, e, f, the right index performs the same three tasks, in fig. 9g, h, i, the right little finger performs and in fig. 9j, k, l, the left thumb.

Suppression of the secondary complex is partially lost when the right index and little fingers are active. When the left thumb is active the task-related suppression is largely lost. The results for the passive task are intermediate.

Effect of Varying the Timing of the Stimulus during the Task

In all the tracking tasks considered so far, the stimulus is given near the middle of the movement. At the standard (medium) velocity the 18-deg movement occupies approximately 1 s. How does the suppression vary at the start and end of a movement? For these experiments we stimulated either at the usual time or around the beginning or end of the tracking movement.

TABLE 2. EFFECT OF VARYING THUMB TRACKING VELOCITY ON THE AMPLITUDE OF SEP COMPONENTS (μV) IN NORMAL SUBJECTS.

Velocity (deg/s) *component*	*0*	*10*	*20*	*40*
Baseline N20	1.12 ± 0.77	1.77 ± 0.82	0.86 ± 0.35	0.89 ± 0.73
N20-P30/45	7.09 ± 2.01	5.26 ± 1.02	4.17 ± 1.36	3.49 ± 1.58
P30/45-N55	10.40 ± 2.48	5.77 ± 1.87	2.63 ± 1.27	2.60 ± 1.71
N55-P80	10.69 ± 8.91	8.51 ± 4.53	7.49 ± 3.11	5.26 ± 2.15
P80-N140	12.23 ± 6.91	12.23 ± 4.84	9.09 ± 3.63	7.89 ± 3.14

Lines and asterisks are placed over each pair of conditions where increasing velocity has resulted in significantly increased suppression, asterisks to the right of their lines. * = $P < 0.05$. ** = $P < 0.01$. *** = $P < 0.001$. 1-tail t-test: n = 5.

Fig. 10a–e gives the results of a representative experiment of this type, where active tracking movements are performed, and it is seen that P45-N55 suppression is as complete 50 ms after the beginning of the movement (after 1 deg of movement) as it is at 500 ms and remains so at least until 50 ms before the end of the movement (1 deg before the end). At 200 ms before the beginning of the movement and 500 ms after the end the form of the evoked potential resembles the control.

If the gating action is exerted on the central connections of the cutaneous afferents from the thumb by other afferent activity related to the thumb, we may next ask, what is the source of that afferent activity? Possible classes of afferent would include muscle spindle afferents from the active muscle or its antagonist, Golgi tendon organ afferents and joint afferents from the interphalangeal joint. The finding that the gating action is independent of load and dependent on velocity would tend to point toward muscle spindle afferents rather than tendon organ afferents, but would not seem to exclude joint afferents.

We attempted to distinguish between these possibilities by blocking one or other of the sources of afferent activity and by vibration of the tendon or flexor pollicus longus. Anæsthesia experiments were done only on ourselves.

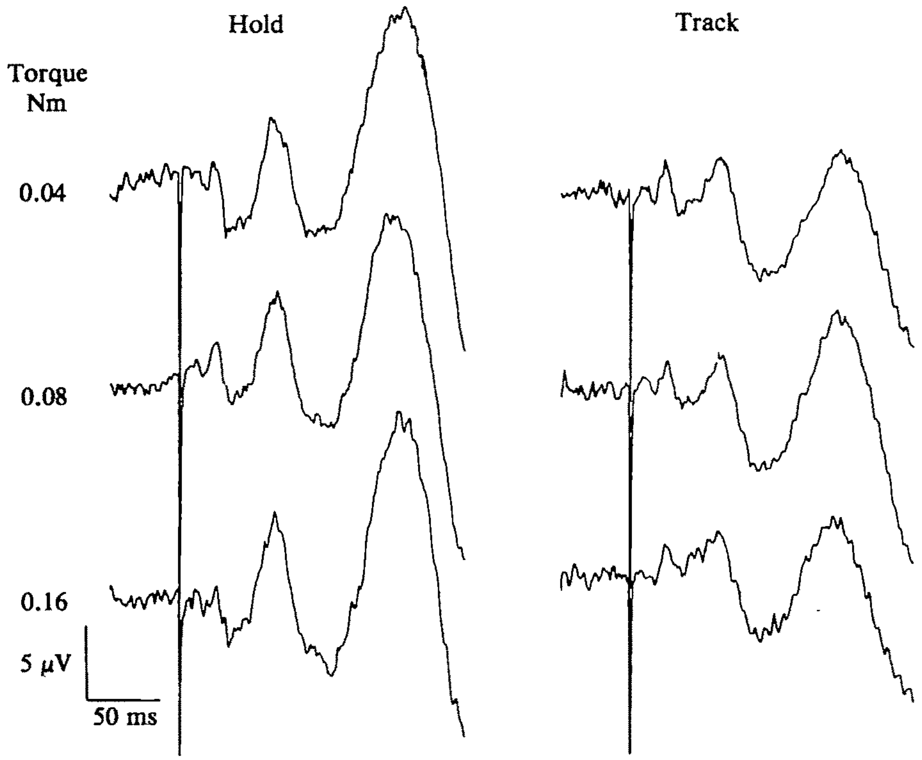

FIG. 8. Variation of load under 'hold' (*left*) and 'track' (*right*) conditions, from 0.04 to 0.16 Nm. 0.16 Nm is about the largest torque that can be comfortably sustained by the thumb for the time (four minutes) required for a run of 64 trials. Intercalated blocks of 64 trials, 3 blocks for each condition. Subject D.R.

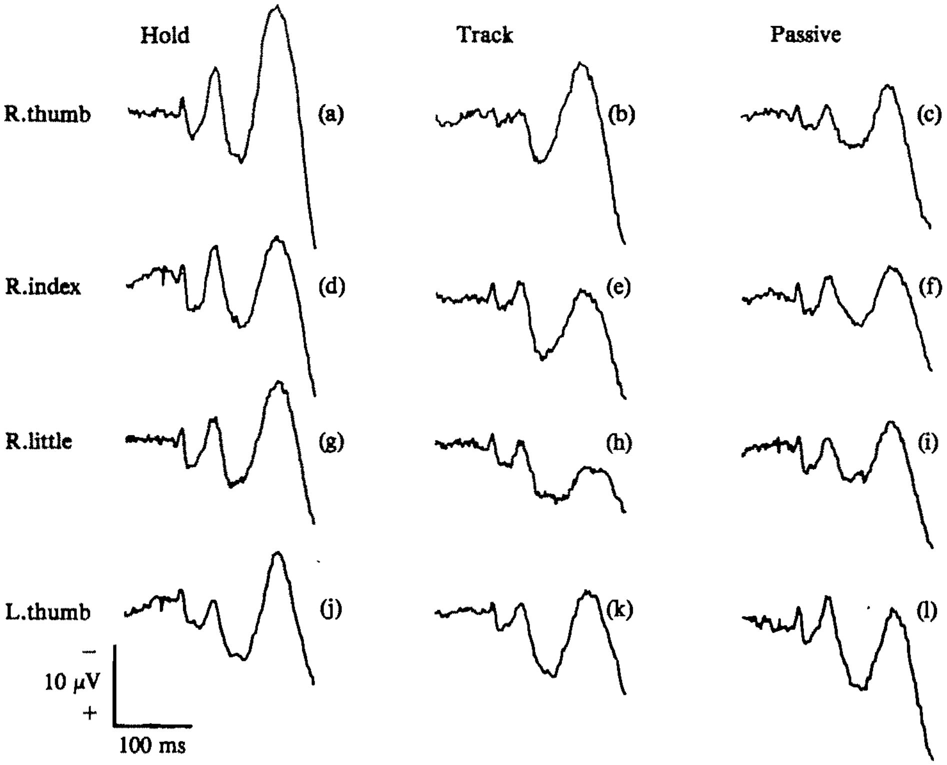

FIG. 9. Effect of varying the active digit. Stimulated digit is the right thumb throughout. Intercalated blocks of 64 trials, 3 blocks for each condition. Subject D.R.

Anæsthesia of Interphalangeal Joint of Thumb

Since the proximal phalanx was clamped and the task performed by flexion of the interphalangeal joint, anæsthesia was induced by infiltration of lignocaine around the joint and the digital nerves just proximal to it, in the presence of a rubber band to prevent spread of anæsthetic more proximally. This effectively abolished local cutaneous and phalangeal joint sensations relating to the task. When passive movements were made, the subject was unaware of them. The digital nerves in the proximal part of the proximal phalanx, in the region of the stimulating cathode, were unaffected.

Fig. 11 gives the results of such an experiment, before and during anæsthesia. The 'hold' response during anæsthesia (11d) is maintained in comparison with the control (11a), confirming that anæsthesia has not spread to the stimulating electrode. Suppression of the secondary complex is about half as complete during digital anæsthesia (11e, f) as in the control experiment (11b, c). Passive movement during anæsthesia (11 f) results in some suppression even though the subject is unaware that his thumb has moved.

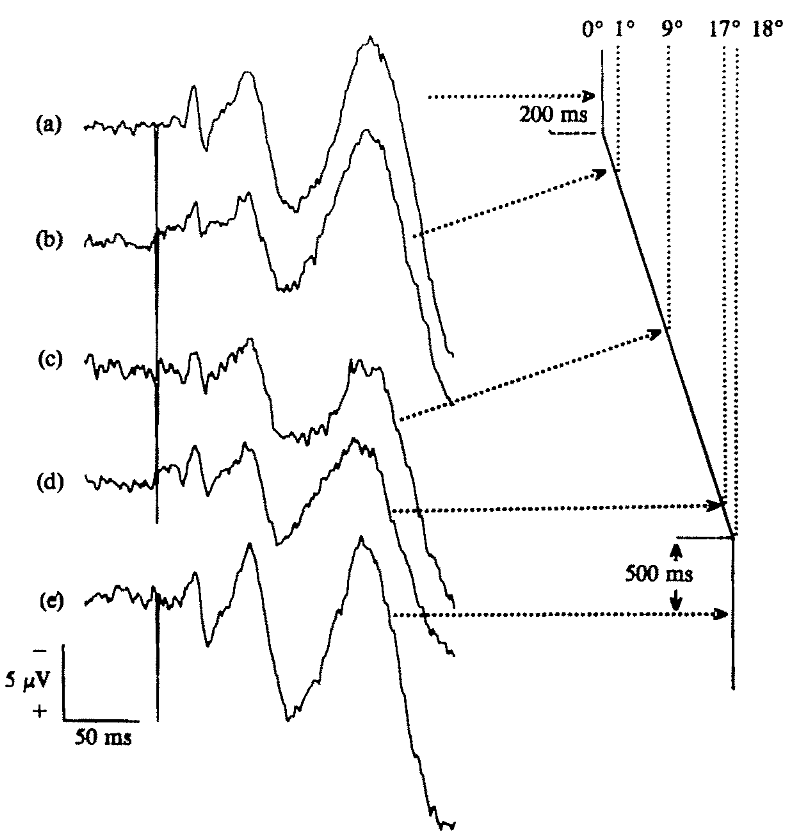

FIG. 10. Effect of varying the timing of stimulation, before, during and after 1 s, 18 deg flexion movement. (a) 200 ms before start, (b) 50 ms after start, (c) 500 ms after start, (d) 50 ms after end, (e) 500 ms after end. Three intercalated blocks of 64 trials for each condition. Subject D.R.

Anæsthesia of the Extensor Pollicis Longus

During thumb flexion in tracking (whether active or passive), the extensor pollicis longus is lengthened, while during 'hold' and 'do-nothing' conditions it is not. One might surmize that a signal from its passively stretched receptors could be serving as the gating signal (Cooper, 1961). We investigated this possibility by performing the usual tasks before and during anæsthesia of the radial nerve just above the elbow, which resulted in a palsy of extension of all digits. We assumed that for the duration of this palsy the extensor pollicis longus was effectively deafferented. We did not test this (for example by attempting to record nerve conduction across the block) because complete anæsthesia lasts only just long enough for the experiment. There was a patch of cutaneous anæsthesia near the base of the thumb, but cutaneous anæsthesia did not extend into the digit, and the 'hold' response is maintained during anæsthesia when compared with the control condition (fig. 12a, d). For radial nerve anæsthesia, the suppression of P45–N55 in the 'track' condition is as complete in the anæsthetized as in the control condition (fig. 12b, e). When the movement is passively induced during radial nerve anæsthesia there is again effective suppression when compared with 'do nothing' (fig. 12c, f). Double anæsthesia (thumb and radial nerve) gave results similar to those of anæsthesia of thumb alone.

Attempted Anæsthesia of the Flexor Pollicis Longus

Since the gating signal during both active and passive movement partly survives anæsthesia of the skin and joint and is unaffected by anæsthesia of the antagonist muscle nerve, it appears that the other source for the gating signal must be the muscle afferents from the flexor pollicis longus itself. The crucial experiment would be to block the nerve to the flexor pollicis longus. Of course, it would not then

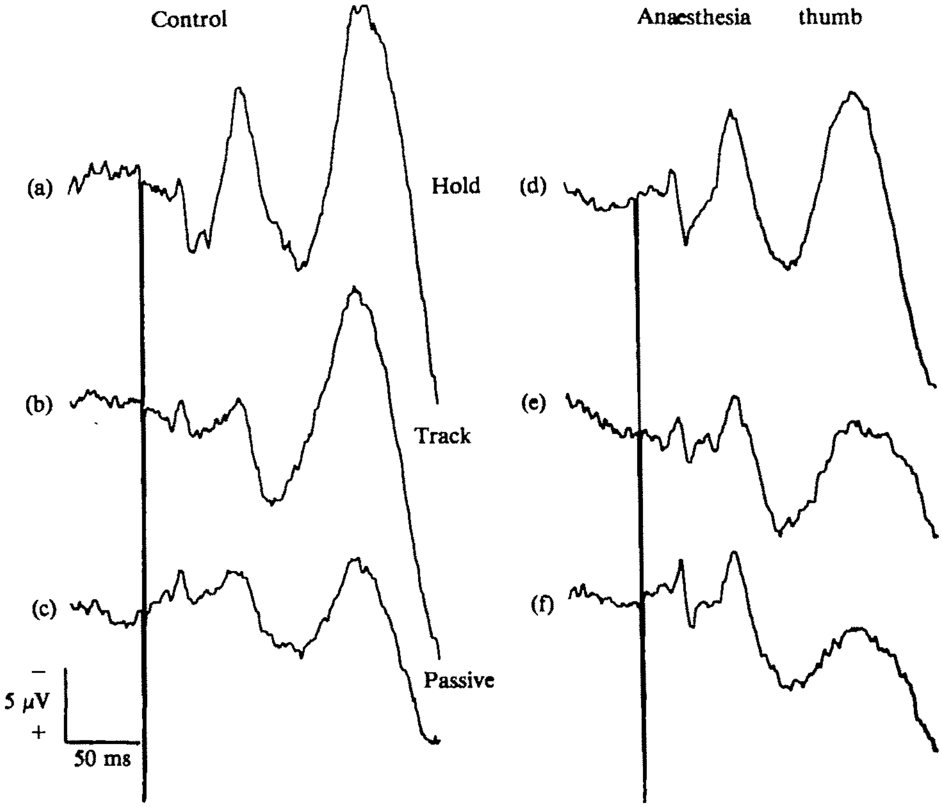

FIG. 11. Effect of anæsthesia of right thumb pad and interphalangeal joint. (a)–(c) control, (d)–(f) anæsthetized, (a), (d) 'hold', (b), (e) 'track', (c), (f) 'passive', 192 trials for each condition, intercalated within but not between anæsthesia conditions. Subject D.R.

be possible to perform the 'hold' or 'track' tasks since the muscle would be paralysed; but the 'do nothing' and 'passive' tasks could still be done.

The difficulty is that the muscle is innervated by a branch of the median nerve (the anterior interosseous nerve) and we have not yet succeeded in blocking this nerve and paralysing the flexor pollicis longus without at the same time affecting the median nerve trunk, in which the fibres from the digital nerves of the thumb have to remain unblocked in order to do the experiment.

Effect of Muscle Vibration

One way to alter the input along afferents from the flexor pollicis longus with at least some selectivity is to vibrate the tendon of the muscle. This induces a high frequency firing mainly of the 1A afferents (Granit and Henatsch, 1956; Brown, Engberg and Matthews, 1967).

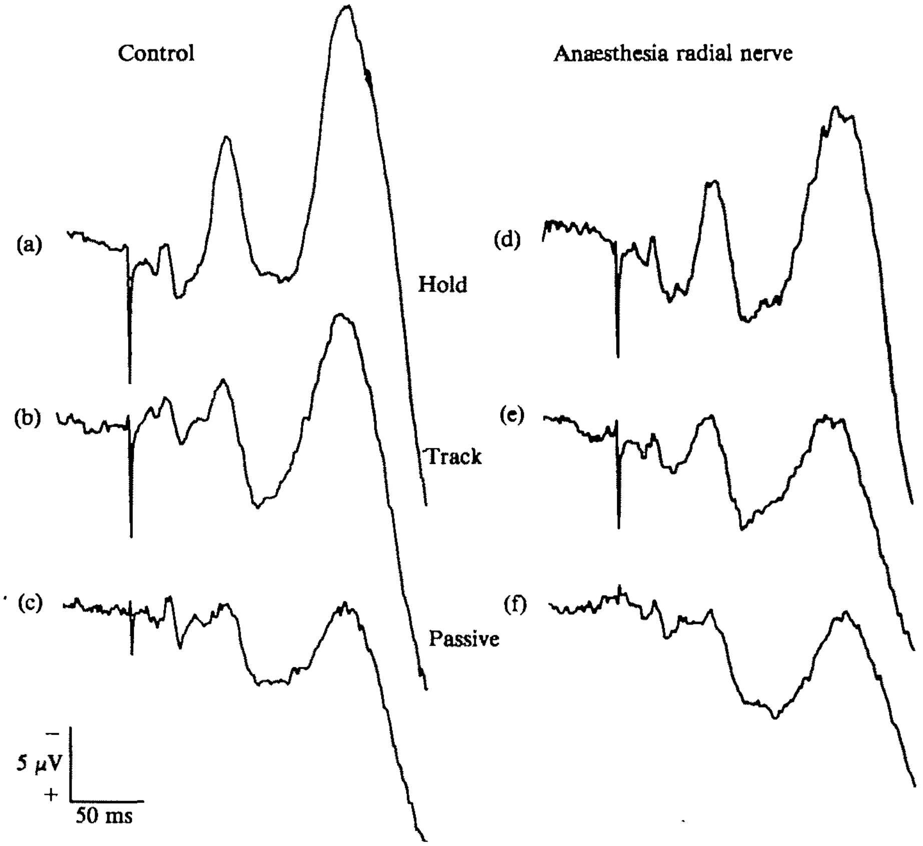

FIG. 12. Effect of anæsthesia of radial nerve at elbow. (a)–(c) control, (d)–(f) anæsthetized, (a), (d) 'hold', (b), (e) 'track', (c), (f) 'passive', 192 trials for each condition, intercalated within but not between anæsthesia conditions. Subject D.R.

The problem is that one does not know whether trains of afferent impulses will act tonically or phasically in operating a gating action, so that one cannot predict whether vibration will mimic or block the effect of muscle shortening. If the gating action is phasic, one might predict that when the vibrator is switched on shortly before the digital nerve shock, it would mimic the effect of muscle shortening, while when the tendon is vibrated continuously the effect of actual muscle shortening on the SEP would be blocked by occlusion.

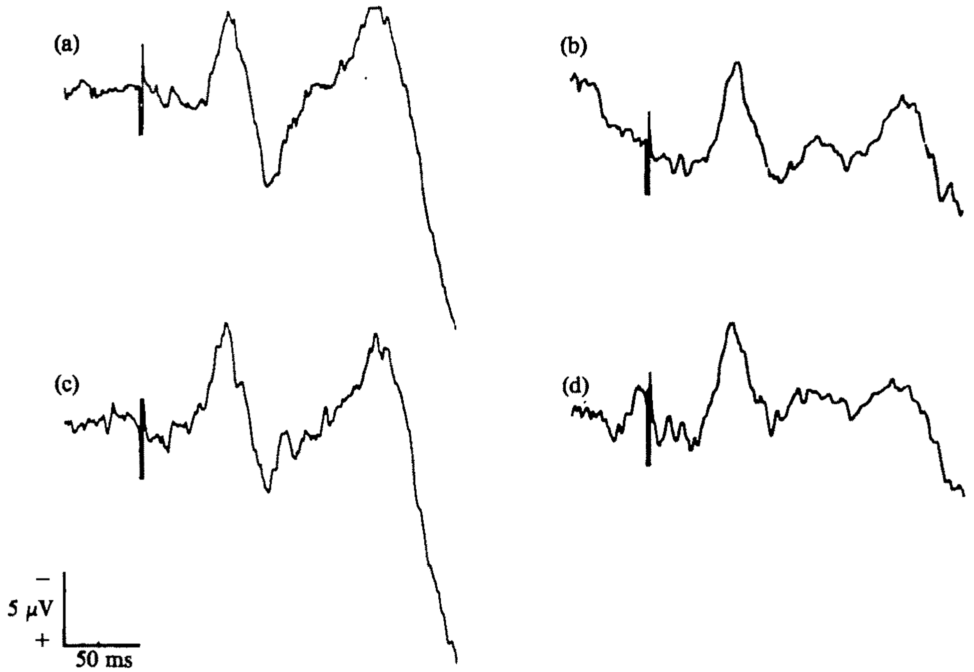

FIG. 13. Effect of vibration of tendon of flexor pollicis longus. Vibration 80 Hz sine, 1 mm p-p, 'hold' condition. (a) no vibration, (b) vibration gated to start 50 ms before stimulus, (c) continuous vibration, (d) vibration gated to start 200 ms before stimulus. Subject M.T.

In the event, it turns out that continuous or gated vibration of the tendon of the flexor pollicis longus fails to alter the primary or secondary responses obtained during the 'hold' conditions (fig. 13a–d, suggesting that steady elevated levels of 1A activity do not effect SEP gating, and that phasic activity in them is not a necessary part of the gating signal. Similarly, continuous vibration during the tracking task failed to abolish the gating action associated with the task (not shown).

Interestingly, the late (N140) wave is inhibited by gated but not by continuous vibration. The reason for this seems obscure. Abbruzzese, Abbruzzese, Favale, Ivaldi and Ratto (1980) reported some decrease in the primary response (N20) induced by hand vibration during stimulation of the median nerve trunk, but they did not average beyond 30 ms.

The vibratory stimulus is not, of course, very specific; the tendon of the flexor pollicis longus is close to the tendons of other muscles and to the radius. It is likely that skin and joint receptors, particularly Pacinian corpuscles in the glabrous skin of the hand, will also be activated.

Electromyographic Responses

Fig. 4 also included the rectified averaged EMG recorded from skin electrodes over the flexor pollicis longus under the four conditions. The muscle is of course silent under the 'do nothing' and 'passive track' conditions, but in the 'hold' and 'track' conditions it exhibits the sequence of excitatory and inhibitory responses first described in detail by Caccia, McComas, Upton and Blogg (1973). The E1, E2, I1 and I2 components of Caccia *et al.* all occur in both 'hold' and 'track' conditions, but the effect of movement on them is slight and inconsistent. The timing of the scalp P45-N55 secondary complex is just early enough that it could be related to the genesis of E1.

The presence of these reflex muscle responses in the conditions of the experiment highlights the problem of whether all the evoked potential components recorded are to be regarded as 'sensory', or whether some of the later EP components are causally more closely related to motor events. Clearly, the scalp potentials are time-locked both to the stimulus and to the muscle response (*see* Discussion).

SEPs in Patients with Lesions Aimed at Thalamic Nucleus VL

In an attempt to determine the pathway through which the secondary complex is derived, we recorded SEPs under the principal conditions ('hold' and 'track') in a small series of 6 patients (aged between 38 and 70 years) with Parkinson's disease (duration five to twenty-five years) who had had left or bilateral stereotaxic lesions aimed at thalamus VL, between three months and twenty-two years before, for alleviation of parkinsonian symptoms, particularly tremor.

The EP recordings were often marred by muscle artefact owing to rigidity, but were nevertheless broadly normal; all the components were present, and the secondary complex was appropriately suppressed during a tracking movement (fig. 14 and Table 3).

It would therefore appear that there is evidence against the notion that the secondary complex might be derived from activity reaching the sensorimotor cortex *via* a recurrent loop involving thalamus VL (*see* Discussion).

DISCUSSION

Modifiable SEP and Muscle Responses

These event-related scalp potentials are called 'sensory' because a stimulus was applied and in none of the tasks was it required that the motor output be changed in response to that stimulus. Nevertheless, performance of the task was in fact

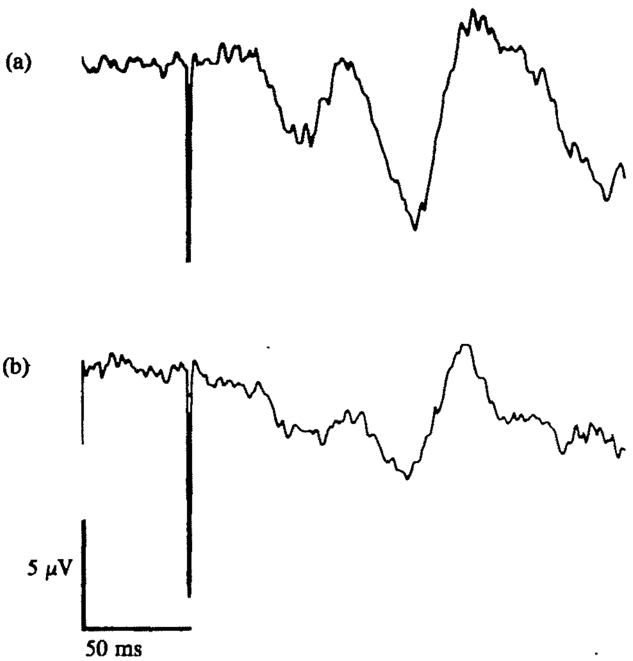

FIG. 14. Grand average of six patients with Parkinson's disease and left stereotaxic thalamotomy. Intercalated blocks of 64 trials, 3 blocks for each condition, one for each patient. (a) 'hold', (b) 'track'. Standard task conditions.

TABLE 3. PARKINSONIAN PATIENTS WITH CONTRALATERAL STEREOTAXIC THALAMOTOMY.

Task component	*Hold*	*Track*
Baseline N20	3.05±2.42	2.43±1.49
N20-P30/45	8.14±1.75	5.43±1.61**
P30/45-N55	7.76±4.08	4.44±0.84*
N55-P80	12.57±8.32	6.42±2.52
P80-N140	15.24±7.61	9.95±6.03

Standard Torque and Velocity (0.08 Nm, 20 deg/s)

* = $P < 0.05$. ** = $P < 0.01$. 1-tail t-test: n = 6.

altered by the stimulus, but reflexly rather than voluntarily. So, is the secondary complex to be regarded as sensory or motor? It is time-locked to both a sensory stimulus and a reflex motor response. The fact that the secondary complex can be present when no reflex muscle response occurs (such as in the 'do nothing' condition, which is the normal circumstance for recording SEPs) is quite compatible with the notion that a reflex input to motor cortex might result in no output when addressing 'switched-off' pyramidal tract neurons (*see* Marsden, Merton and Morton, 1981). In the 'track' condition the EMG reflex components are all present while the secondary complex diminishes. This would seem to leave open the possibility that the secondary complex could be causally related to the reflex muscle responses. Conrad and Aschoff (1977) reported that a wave of muscle activity which they called the 'C' response (occurring at 60 to 90 ms after median nerve stimulation) was increased during movement of the finger. Their response seems to be closely related to the E1 response of Caccia *et al.* (1973), since it was also found to occur on stimulation of a digital branch.

Source of the Primary and Secondary EP Complexes

Before attempting to explain the effect of task on the primary and secondary cortical complexes, it would be helpful to have a clear notion as to how they arise. The primary complex (N20-P30) seems relatively straightforward; it arises at the region of the somatosensory area, and begins only 2 to 3 ms after components that have been identified as arising in the thalamocortical radiation (Cracco, 1972). It seems likely that it represents postsynaptic activity in the primary somatosensory cortex (Arezzo, Legatt and Vaughan, 1979). Goff, Allison, Williamson and Vangilder (1979) suggest that the N20–P30 component arises in Area 3*b*.

The source of the secondary (P45–N55) complex is much more obscure. Our localization experiments (in agreement with Goff *et al.*, 1977, but *see* Goff *et al.*, 1979), suggested that its generator is placed anterior to the generator of the primary complex. The effect of graded strengths of stimulation showed that the secondary complex is not likely to be caused by the late arrival of activity in slow afferent fibres. It seems unlikely that it arises through the delay of afferent activity in polysynaptic reticular pathways in the brain-stem (analogous to the 'secondary response' described by Forbes and Morison (1939) in the deeply anæsthetized cat), because a late response of that sort would be expected to be diffusely distributed, which this response is not.

It does seem most unlikely that the action of a sensory volley could be sequestered at the site of the primary response in the somatosensory cortex for 25 ms, only then to emerge as a synchronized wave. An attractive explanation would be that after initial cortical processing (N20-P30) the volley is dispatched to another part of the brain for use or further processing, from which it returns to the cortex on a pathway directed to the motor area, perhaps in a form that has been rendered suitable for incorporation into the present motor cortical output.

There are two prominent feedback loops of this kind; one is the cerebello-thalamo-cerebral loop, feeding from sensorimotor cortex back to Area 4 (Evarts and Thach, 1969; Phillips and Porter, 1977), with a loop latency in the cat of about 10 ms (Allen and Tsukahara, 1974). The other is the cortico-striato-pallido-thalamo-cortical loop (Kemp and Powell, 1971), which also feeds back to Area 4, but whose loop latency is unknown, and may well be too long.

It was because both of these loops include thalamic nucleus VL that we investigated parkinsonian patients who had stereotaxic lesions aimed at VL. The negative (that is, normal) results that we obtained suggest either that their lesions were too small to interrupt the pathway, or that being placed so as to interrupt the pallidal feedback they failed to interrupt the cerebellar feedback, or else that neither of these feedback loops is essential for the generation of a secondary SEP complex.

Pagni (1967) in nucleus VPL and Fukushima, Mayanagi and Bouchard (1976) in nucleus VC have found no evidence of a thalamic component immediately preceding the secondary cortical complex, but Fukushima *et al.* did find such responses in the nuclei CM and VL, although they were not strictly contralateral (unlike the early response in nucleus VC, the primary relay nucleus). The wide and bilateral distribution of the late responses described by Fukushima *et al.* may explain why the gating action was not lost in our patients.

Source and Site of the Gating Action

There is evidently more than one site where the centripetal flow of sensory information can be gated. Transmission at the dorsal column nuclei as evidenced by gross lemniscal response is attenuated by active but not by passive movement (Ghez and Pisa, 1972; Coulter, 1974), and may be inhibited by cortical or reticular stimulation (Dawson, 1958).

In the VB thalamic relay of the cat, both excitation and inhibition have been found in response to pyramidal tract stimulation (Tsumoto, Nakamura and Iwama, 1975); joint afferents tended to be excited and hair afferents to be inhibited.

Ghez and Pisa (1972) found inhibition of the lemniscal response to superficial radial nerve stimulation in awake cats; the inhibition increased with increasing velocity of movement but not with increasing load. This (average 20 per cent) inhibition must presumably be occurring at the dorsal column nuclear level.

However, a much more profound gating action can occur during a later stage of sensory processing, between the primary and secondary cerebral responses. Because the gating we observe occurs in most subjects during both active and passive movements, it must be controlled by other signals from the periphery, rather than by efference copy. Anæsthesia experiments suggest that signals from the skin, joint and shortening muscle are involved, but not signals from the antagonist muscle. The gating action is ‘focused’, such that it is most profound when the same digit is both stimulated and moving. It is reduced when the moving digit neighbours the stimulated one, and lost when movement and stimulation occur in different limbs. Our finding that the gating action is unrelated to load, which is consistent with the results of Ghez and Pisa, is not so easy to reconcile with the finding of Hulliger and Vallbo (1979) that during an isometric or isotonic shortening (but not lengthening) movement primary muscle spindle afferent activity increased with increasing load, and is no greater during shortening than in isometric conditions. It would seem that the primary muscle spindle afferent signals are not the gating signals; and this might explain our failure to obtain clear-cut results from muscle tendon vibration.

Although the *source* of at least part of the gating signal is peripheral, the site at which the action is *exerted* is evidently central, because of the clear differential effect of movement on the primary and secondary cerebral responses. The exact site at which this gating action is exerted is unclear since the pathway followed by the volley from 30 to 45 ms post-stimulus is unclear. Although it seemed likely that the cerebrocerebellar feedback loop would be involved, we have obtained no evidence yet that this is the case. Thalamic nucleus VL has, however, been put forward in the past as a site at which peripheral sensory inputs could gate the transmission of activity in the cerebrocerebellar feedback loop (Massion, 1968).

SUMMARY

1. Somatosensory evoked potentials from electrical stimulation of the digital nerves of the right thumb have been recorded during the performance of various motor tasks in eight normal subjects.

2. The N20-P30 primary cortical response is only moderately affected by task context, while the P45-N55 secondary response is markedly 'gated' by movement of the stimulated digit. The late N140 vertex is variable.

3. In most subjects, active and passive movements are about equally effective in suppressing the secondary complex; but in one, passive movement has come to be rather less effective than active.

4. Secondary response suppression occurs in proportion to the velocity of the movement of the thumb, up to a velocity of 20 deg/s.

5. Secondary response suppression is unrelated to load in the range 0 to 0.16 Nm.

6. When the stimulus is timed to occur at various points in movement, secondary complex suppression occurs at all stages; but there is little or no suppression when stimulation is timed at 200 ms before the start of or 500 ms after the end of a movement.

7. Secondary response suppression is maximal when the same digit is both moving and shocked. When the right index or little finger are moved instead, the right thumb being stimulated, suppression is less; when the left thumb moves, no suppression is seen.

8. Secondary response suppression is reduced but not lost if the skin and

interphalangeal joint of the thumb are anæsthetized distal to the stimulating electrodes.

9. Secondary response suppression is unimpaired when the radial nerve is anæsthetized, paralysing the finger extensors.

10. In an attempt to identify the course taken by the afferent volley between the primary and secondary responses, and to identify the gating site, we recorded the responses in six patients with Parkinson's disease who had undergone thalamotomy. Their secondary responses were present, and gated in the normal way.

11. We are unable to confirm whether the secondary response represents the re-arrival at cortical level of a volley that has traversed the cerebrocerebellar loop.

12. We confirm that the secondary complex is located a little anterior to the primary cerebral response.

13. We conclude that a gating action is exerted in the brain on somatosensory afferent activity, after it first reaches the cortex, and that this gating action associated with movement is controlled by other afferent signals from the stimulated limb, and particularly from the stimulated digit.

ACKNOWLEDGEMENTS

We should like to thank Professor C. D. Marsden in whose Department of Neurology these experiments were performed.

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(*Received January 27, 1981*)

Brain (1981), **104**, 493-511

DISORGANIZATION AND REORGANIZATION OF COGNITIVE AND SENSORIMOTOR FUNCTIONS IN CEREBRAL COMMISSUROTOMY

COMPENSATORY ROLES OF THE FOREBRAIN COMMISSURES AND CEREBRAL HEMISPHERES IN MAN

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INTRODUCTION

CONCEPTS in human neuropsychology have arisen largely from early experience with naturally occurring brain lesions, supplemented by extrapolations from animal experimentation. Studies of patients with recently developed surgical procedures, including hemispherectomy and cerebral commissurotomy have provided unique data bearing on unresolved historical controversies. This paper reports results of an ongoing, longitudinal study of commissurotomy subjects, in the light of results obtained in similar studies of a large group of hemispherectomy patients tested with the same neuropsychological tests. We suggest that the findings in comparisons of initial and later comprehensive neuropsychological studies of children and adults with commissurotomy and with hemispherectomy afford bases for reconciling many of the diverse and often paradoxical findings reported in subjects with focal lateralized brain insults.

Comparisons of effects of hemispherectomy for brain tumour in adults and for intractable seizures in patients with lateralized infantile epileptogenic lesions reveal marked differences. Removal of an adult left or right hemisphere that had developed normally until the growth of a tumour resulted in reciprocal syndromes. Left hemispherectomy resulted in severe and persisting impairment of language and verbal reasoning abilities with relative sparing of nonverbal abilities *versus* the

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reciprocal syndrome of severe and persisting impairment of nonverbal functions with sparing of language functions after right hemispherectomy. In contrast, removal of either hemisphere in patients with infantile lateralized lesions has generally been consistent with the development of normal or even superior adult language and nonverbal reasoning capacities (Smith, 1966, 1969, 1972, 1975, 1978, 1979, 1981*a*, *b*); Smith and Burklund, 1966; Smith and Sugar, 1975; Burklund and Smith, 1977).

Thus, following right or left hemispherectomy for early laterialized epileptogenic lesions, the remaining hemisphere and other intact residual structures can provide for the development of both verbal and nonverbal reasoning. The significant improvement of language functions during the limited periods of survival following left hemispherectomy for tumour indicates that, although diminished, the plasticity of the human brain continues into the later decades of life. Similarly, several intracarotid sodium amytal studies have indicated a significant role of the right hemisphere in recovery of speech following aphasiogenic left hemisphere lesions in older adults (Mempel, Srebrezynska, Subszynska and Zarski, 1963; Kinsbourne, 1971; Czopf, 1973). Thus, one of the critical factors determining the sequelæ of lateralized lesions as well as hemispherectomy would appear to be the intactness of the opposite hemisphere (Smith, 1981*b*). In cases with lateralized lesions, moreover, the integrity of interhemispheric compensatory mechanisms is a consideration, as suggested in earlier reports by Russell and Espir (1961) and Russell (1963). The role of the forebrain commissures, particularly their compensatory potential, continues to be a subject for unresolved historical controversies and academic speculation.

Following the reintroduction of cerebral commissurotomy as a treatment for intractable seizures (Bogen and Vogel, 1962, 1963, 1975; Bogen, Fisher and Vogel, 1965; Bogen, Sperry and Vogel, 1969; Luessenhop, de la Cruz and Fenichel, 1970; Wilson, Culver, Waddington and Gazzaniga, 1975; Wilson, Reeves, Gazzaniga and Culver, 1977; Wilson, Reeves and Gazzaniga, 1978; Amacher, 1976), studies specifically concerned with interhemispheric transfer have contributed to greater understanding of the neocommissures (Sperry, Gazzaniga and Bogen, 1969). Studies of single hemisphere capabilities, including memory for lateralized input have also been reported (Milner and Taylor, 1972; Kumar, 1977). However, the extent to which cerebral commissurotomy affects a variety of other functions, including memory for nonlateralized stimuli, remains controversial.

Citing impairment of memory in post-operative tests of 8 patients with complete and 2 with frontal commissurotomy, Zaidel and Sperry (1974) concluded that the forebrain commissures could play an important role in bilateral cerebral mechanisms mediating certain mnestic functions. However, noting the absence of pre-operative studies in the patients reported by Zaidel and Sperry (1974), LeDoux, Risse, Springer, Wilson and Gazzaniga (1977) attributed the reported memory deficits to presumed persisting effects of unspecified extra-callosal damage which had been present pre-operatively. Based on a case with callosotomy with pre-operative testing, they reported higher post-operative scores in various tests of intellectual and memory functions. They concluded 'these controlled observations . . . unequivocally argue that commissurotomy does not necessarily produce cognitive deficits' (p. 101).

These and other diverse findings in studies of patients with frontal or complete commissurotomy are qualified by numerous interacting factors. Differences between the specific surgical procedures used in these two studies were noted by Wilson *et al.* (1977). There are also differences between the callosotomy (sparing the anterior commissure) in the patients reported by LeDoux *et al.* (1977) and by Gazzaniga, Volpe, Smylie, Wilson and LeDoux (1979), section of only the body of the corpus callosum (Dimond, Scammell, Brouwers and Weeks, 1977; Jeeves, 1979; Winston, Cavazutti and Arkins, 1979), frontal commissurotomy leaving the splenium intact (Gordon, Bogen and Sperry, 1971; Wilson *et al.*, 1977; Ozgur, Johnson, Smith and Bogen, 1977), and complete commissurotomy (in which all forebrain commissures are divided).

Numerous reports have compared the post-operative findings in humans with the results of commissurotomy in animal experiments. Since studies of effects of surgery in animals are usually limited to one or two years post-operatively, comparisons of such studies with long-term effects of commissurotomy are obviously qualified. More important is the condition of the brain as a whole (Smith, 1979, 1981*a*, *b*). In contrast to the presumed intact animal brain in experimental studies, the presence of severe and frequent seizures despite the use of various anticonvulsant medications for extended periods before operation reflects varying combinations of the diverse underlying epileptogenic brain insults and associated pre-operative pathological features. Moreover, as the reports by Bogen (1976) and Wilson *et al.* (1977) indicate, post-operative complications can introduce further qualifying factors. Comparisons of pre-operative and post-operative test performances are further confounded by the effects of anticonvulsant medication (usually reduced after operation) and by varying effects of operation (elimination, reduction or no change) on seizures. Finally, as in studies of hemispherectomy (Smith, 1966, 1969, 1972, 1975, 1978, 1981*a*, *b*), the effects of commissurotomy may vary with age, time, and other factors, especially the capacities of the residual brain structures for reorganization of intra- or interhemispheric mechanisms.

At the invitation of J.E.B. in 1967, one of us (A.S.) administered in 1967 and again in 1976 the Michigan Neuropsychological Test Battery to a series of patients with complete and frontal commissurotomy. This report summarizes the major findings in 10 patients with complete commissurotomy and 2 with frontal commissurotomy, including pre-operative and post-operative neuropsychological tests of one patient (M.K.). The availability of pre-operative Wechsler IQs (1939, 1949 and 1958) permitted comparisons in 9 of the patients.

The accumulated data on the 12 patients, including pre-operative, initial and long-term post-operative studies, afford bases for evaluating the long-term deficits following division of the forebrain commissures. Of greater importance, perhaps, these longitudinal studies of 12 commissurotomy patients add unique data to the accumulating evidence for certain principles underlying the reorganization of brain functions after lateralized cerebral lesions and hemispherectomy in children and adults (Smith, 1981*a*).

SUBJECTS

The population consisted of 10 patients with complete and 2 with frontal commissurotomy. Surgery was performed by Dr P. J. Vogel and Dr J. E. Bogen. Complete commissurotomy consisted of transections of the entire corpus callosum, the anterior and hippocampal commissures and, when present and visualized, the massa intermedia. Table 1 summarizes the reported medical histories of each patient including the nature of initial cerebral trauma before onset of seizures; age at the time of trauma, at onset of seizures, and at operation; and extracommissural damage revealed in pre-operative and post-operative neurological, electroencephalographic, and in 2 cases, CAT studies (Bogen, 1969; Gordon *et al.*, 1971; Bogen and Vogel, 1975; Bogen, 1976; Botez and Bogen, 1976). As noted above, the condition of the brain as a whole before and after commissurotomy is an important factor determining the nature, severity and duration of the post-operative sequelæ. That is, the status of each of the two cerebral hemispheres before and after their disconnection determines the capacities for reorganization of compensatory cerebral mechanisms as reflected in both the initial and later changes in various functions. Table 1 shows the emergence of seizures at ages ranging from 3 to 38 years of age. Since such seizures proved intractable despite the use of anticonvulsant medications from 3 to 20 years before operation (mean duration 14.9 years), the extra-callosal damage in all twelve patients probably reflects, in addition to the initial lateralized or bilateral epileptogenic brain insults, varying degrees of added damage to the brain as a whole as a result of the prolonged severe seizures before surgery.

Pre-operative and/or post-operative studies indicated greater involvement of the right than left hemisphere in 7 patients (L.B., N.W., R.Y., J.M., N.G., W.J. and M.K.) including pre-operative right hemisphere structural damage (Group RHS) in 4 (J.M., N.G., W.J. and M.K.). Greater involvement of the left than right hemisphere but without evidence of pre-operative structural left hemisphere damage was recognized in 5 (A.A., C.C., R.M., N.F. and D.M.). In one patient (A.A.) a small area of the right parietal region was damaged when two bridging veins were interrupted during commissurotomy. In another (N.F.), there was an episode of aphasia, right hemiplegia, and right-sided clonic seizures on the seventh day after frontal commissurotomy.

The term 'structural damage' is used throughout this paper to designate the specific instances in which neurosurgical and/or radiological observations afforded definitive evidence of gross anatomical lateralized lesions.

METHODS

Tests Administered

The Michigan Neuropsychological Test Battery (MNTB) used in studies of 75 patients with hemispherectomy since 1965 was introduced in studies of the 12 patients with commissurotomy in 1967. These studies included pre-operative tests of one patient (M.K.). Post-operative tests provided measures of verbal and nonverbal, cognitive, manual motor and somatosensory functions from four to sixty-seven months post-operatively. At the time of follow-up studies in January, 1976, one (W.J.) had died, and one (M.K.) was unco-operative. Re-examinations of the 10 remaining patients after a seven- to eight-year interval permitted assessments of further changes on the WAIS and other tests at seven to thirteen years post-operatively.

TABLE 1. MEDICAL SUMMARIES OF 10 PATIENTS WITH COMPLETE AND 2 WITH FRONTAL COMMISSUROTOMY

Patient and commissurotomy procedure	*Type of trauma*	*Age at*			*Date of op.*	*Extracommissural pathology*
		Trauma	*Onset of seizure*	*Surgery*		*Hemispheric involvement/Evidence*
Complete						
C.C.	Birth?	0	10	13	27/3/65	Left/Pre-op. EEG[1]; post-op. neurol. exam.[2]
A.A.	Birth	0	5	14	14/10/64	L+R: L > /Pre-op. EEG[1]; post-op. neurol. exam. and seizures[2]; infarction of R parietal region (surg. complication)[1]
R.M.	Birth?	0	12	27	14/3/66	R+L: L > /Pre-op. EEG[1]; post-op. EEG[3]
L.B.	Birth	0	3	13	1/4/65	R+L: R > /Pre-op. EEG[1]; post-op. seizures[1]; post-op. neurol. exam.[2]
R.Y.	CHI*	13 yrs	17	43	7/3/61	R/Prodromal seizures sign[1]; post-op. neurol. exam.[2]
N.W.	'Idiopathic'	< 3 yrs	3	36	12/12/66	R+L: R > /Pre-op. EEG and post-seizure neurol. sign[1]; post-op. neurol. exam. and CAT scan[2]
N.G.	Prem. birth	0	18	30	5/9/63	R lesion and L focus: R > /Skull x-ray and EEG[1]; post-op. neurol. exam.[2]
W.J.	CHI*	Apx. 31–32	38	48	6/2/62	R+L: R > /Pre-op. EEG[1]; marked right front. cerebral atrophy noted during op.[1]
J.M.	CHI*	Apx. 15	16	36	2/2/68	R+L: R > /R temporal lobectomy (1955), EEG[1]; post-op. neurol. exam. and CAT scan[2]
M.K.	Febrile ill.	3 yrs	9	29	18/10/67	R+L: R > /Pre-op. EEG, seizures[1]; mild R hemicerebral atrophy noted during op.[1]; L homonymous hemianopia (neuropsych. test)
Frontal						
D.M.	CHI*	11 yrs	11	23	31/7/68	R+L/Pre-op. EEG, neurol. signs; post-op. seizures[4]
N.F.	'Idiopathic'	< 14 yrs	14	26	17/1/69	R+L: L > /Pre-op. EEG[4]; post-op. complications 7th day, resulting in flaccid hemiplegia on R side, presumably from stroke[4]

* CHI = Closed head injury. [1] (Bogen and Vogel, 1975) [2] (Botez and Bogen, 1976) [3] (Bogen, 1976) [4] (Gordon *et al.*, 1971).

Either the WAIS, Wechsler-Bellevue (W-B), or WISC, depending on the age of the patient at testing, had been administered pre-operatively to 9 patients when all forebrain commissures were presumably intact.

Visual Organization Test (*VOT*). The Hooper VOT (1958) consists of line drawings of common objects (for example, fish, hammer, truck, broom) that have been cut up with the pieces rearranged in random patterns. Like the Wechsler Block Design and Object Assembly subtests, the VOT provides a measure of visual-spatial-organizational abilities. However, unlike these two subtests, the pieces shown on the picture of each cut-up object cannot be moved. The test is untimed and consists of thirty items.

Raven Coloured Progressive Matrices (*RCPM*). Developed by Raven (1956), this test measures nonverbal reasoning in visual modes of thought. Patients are required to examine a pattern with one section missing, then choose the one from six alternatives that would complete the pattern. The RCPM is untimed and consists of thirty-six items.

Visual Retention Test (*VRT*). The Visual Retention Test (revised) was designed to measure visual memory and constructional abilities (Benton, 1963). Each of ten cards (Form C) with one or more designs is exposed for ten seconds (Administration A) and then withdrawn, followed by immediate reproduction from memory by the patient. To differentiate impairment of visual memory from constructional disabilities, the patient is then asked to copy each of the same designs (Administration C).

Purdue Pegboard (*Purdue*). This test of manual dexterity was adapted by Costa, Vaughan, Levita and Farber (1963) for determining the presence and laterality of cerebral lesions. Patients are instructed to insert pegs for sixty seconds, one at a time, and as rapidly as they can, in a column of holes in a pegboard, starting with the preferred hand. The test is then repeated with the non-preferred hand, and then with both hands simultaneously, with the examiner recording the number of pegs inserted in thirty and sixty seconds.

Symbol Digit Modalities Test (*SMDT*). The Symbol Digit Modalities Test (Smith, 1973) is a simple substitution test, reversing the format of the WAIS Digit Symbol subtest. In the Digit Symbol test the substitution responses are geometric designs which can only be written, whereas responses to the SDMT consist of numbers. The patient is given ninety seconds to make as many written substitutions as possible. This is followed by the oral form in which the patient speaks instead of writes the numbers for another ninety-second interval, with the examiner recording the responses. Thus, the SDMT permits comparisons of efficiency in performance on the same mental test in two different modalities: writing and speaking. The SDMT has proven to be the most sensitive single indicator, in the Michigan Neuropsychological Test Battery, of cerebral dysfunction, and of changes in the clinical picture with time and/or therapeutic intervention. Such changes are usually in the form of increased or decreased speed and efficiency in written and oral substitutions rather than increases or decreases in errors.

Peabody Picture Vocabulary Test (*PPVT*). The Peabody Picture Vocabulary Test, designed as a measure of auditory receptive vocabulary by Dunn (1959), requires the patient to select one of four pictures on a page corresponding to the word spoken by the examiner. It is an untimed test and is terminated when the patient fails in six of any eight words in the standardized word list which is graduated for difficulty.

Single and Double Simultaneous (*Face-Hand*) *Stimulation Test* (*SDSS*). This test of somatosensory functions, developed and standardized by Centofanti and Smith (1979), is a refinement of the earlier Double Simultaneous Stimulation Test (Bender, 1945). The patient is seated, asked to close his/her eyes and place the palm of each hand on the ipsilateral thigh. Patients are then required to indicate by pointing where they had been touched by the examiner after single or double simultaneous stimulations of the right and/or left cheek and/or hand. Twenty trials (eight single and twelve double simultaneous stimulations) are administered.

Memory for Unrelated Sentences (*MUS*). While the WAIS Digit Span subtest provides a measure of immediate auditory memory for non-meaningful series of random numbers, the MUS (Ostreicher, 1973) measures immediate auditory memory for semantic/syntactic materials. Patients are requested to immediately repeat after the examiner each of ten sentences of increasing length. The test is terminated after errors are made in two consecutive sentences, and the patient's score consists of the largest number of syllables in any sentence.

RESULTS

Table 2 presents comparisons of pre-operative and post-operative test scores for the twelve patients. The marked heterogeneity in this small sample of patients with respect to the ætiology and locus of epileptogenic lesions, age at onset, associated extra-callosal pathology and other significant variables indicated above precluded statistical analyses of the data. However, despite the small numbers, the findings reveal certain consistencies in comparisons of subgroups differentiated for specific factors.

Comparisons of Pre-operative and Post-operative Wechsler IQs of 7 Complete Commissurotomy and 2 Frontal Commissurotomy Patients

Pre-operative Wechsler scales, available for 9 patients, revealed a mean Full-scale IQ of 90.2 (range 74 to 113) with comparable mean IQs for the 7 with complete (90.7) and the 2 with frontal commissurotomy (88.5). As Table 2 shows, of the 9 patients tested pre-operatively, Wechsler Full-scale IQs were in the normal range in 4 cases (3 complete, one frontal commissurotomy), in the dull normal range in one case, and in the borderline or retarded range in the remaining 4. Comparisons of pre-operative and initial post-operative Full-scale IQs show a mean decline of 8.8 points (range 0 to 21 points).

Initial and Long-term Post-operative Comparisons of Wechsler IQs

Initial studies, from four to sixty-seven months post-operatively, revealed a mean Wechsler Full-scale IQ of 80.8 (range 65 to 109). In long-term follow-up studies of 10 patients (8 complete commissurotomies, 2 frontal commissurotomies) from seven to thirteen years post-operatively, only negligible changes (1.9 points) in mean IQs occurred. Although comparisons of mean Full-scale IQs indicate no appreciable changes, one patient (N.W.) showed a long-term gain of 14 points (from 81 to 95), while Full-scale IQs of R.M. and C.C. declined.

TABLE 2. FOLLOW-UP NEUROPSYCHOLOGICAL STUDIES OF 10 PATIENTS WITH COMPLETE AND 2 WITH FRONTAL COMMISSUROTOMY

	L.B.				*N.W.*		*R.Y.*		*J.M.*			*N.G.*			*W.J.*[3]	
	Pre-op.		*Post-op.*		*Post-op.*		*Post-op.*			*Post-op.*			*Post-op.*			
	1	*2*	*1*	*2*	*1*	*2*	*1*	*2*	*Pre-op.*	*1*	*2*	*Pre-op.*	*1*	*2*	*Pre-op.*	*Post-op.*
Verbal IQ	115	119	113	109	87	98	94	98	106	104	94	79[5]	79	75	111	110
Performance IQ	108	108	102	110	75	92	69		95	74	76	74[5]	64	71	100	84
Full scale IQ	113[1]	113[1]	109	110	81	95	82	87	102	90	86	76[2,5]	71	72	106	99
Vis. Organization			28.5	29.5	20	22	17.5	13.5		17	14.5		23.5	23.5		17
Raven Col. Matrices			32	34	18	13	18	13		16	19		16	24		13
Benton Vis. Reten.			6	8	2	4	3	3		5	4		3	0		3
Benton Des. Copy			10	10	9	6	4	6		5	7		10	7		8
Purdue Pegboard R			10/23	11/21	16/32	15/28	16/30	14/26		15/26	13/26		13/25	13/27		8/16
Purdue Pegboard L			8/15	8/15	3/13	12/25	*11/25	13/26		11/21	9/20		8/17	8/20		8/17
Purdue Pegboard Both			—	8/17	—	11/22	—	11/20		—	10/19		—	10/19		—
Symbol Digit written			34	30	15	18	2	9		13	19		17	5		4
Symbol Digit oral			39	42	17	28	0	9		14	28		15	22		17
Peabody Raw Score				132+	102	112	—	92		130+	135+			94		
SDSS (Face-Hand)			B	N	B (L > R)	—	—	B (L > R)		B	B (L > R)		B	B		B
Memory Unrel. Sent.			—	27	—	30	—	30		—	31		—	30		—
Hand/eye			R/R	R/R	R/R	R/R	R/L	R/R		R/R	R/R		R/L	R/R		R/R
Age/sex			15-4/M	23-8	39/F	45-8	43/M	51		37/F	44-4		34-3/F	42-6		55-9/M
Education			8	12	16		8			10			12			12
Test date	18/3/65		18/9/67	8/1/76	23/5/69	2/1/76	23/9/67	4/1/76	31/1/68	24/5/69	6/1/76		18/9/67	3/1/76	15/1/58	19/9/67
Years post-op.			2-5	10-9	2-5	9-1	1-6	9-10		1-3	8		4-0	13-2		5-7

	M.K.[4]		*A.A.*			*C.C.*			*R.M.*		*N.F. (Frontal)*			*D.M. (Frontal)*		
				Post-op.			*Post-op.*		*Post-op.*			*Post-op.*			*Post-op.*	
	Pre-op.	*Post-op.*	*Pre-op.*	*1*	*2*	*Pre-op.*	*1*	*2*	*1*	*2*	*Pre-op.*	*1*	*2*	*Pre-op.*	*1*	*2*
Verbal IQ	89	86	80	75	77	73[2]	61	59	80	68	93[2]	77	82	70	68	72
Performance IQ	88	60	72	75	72	83[2]	70	61	72	72	108[2]	86	89	87	77	78
Full scale IQ	88	74	74	74	74	76[2]	65	58	75	68	101[2]	80	84	76	71	73
Vis. Organization	26	19		21.5	25.5		20.5	17.5	24	25		26	24.5		21	25
Raven Col. Matrices	34	18		21	25		25	21	18	22		29	29		28	24
Benton Vis. Reten.	10	1		3	4		2	2	4	2		4	6	8	4	6
Benton Des. Copy	10	7		10	5		9	7	10	8		9	10		10	9
Purdue Pegboard R	10/21	11/19		7/12	6/12		13/22	10/19	8/18	5/8		8/16	8/17		10/20	10/20
Purdue Pegboard L	4/12	6/12		9/17	9/18		11/23	11/19	8/15	6/13		11/22	11/20		9/20	10/19
Purdue Pegboard Both	—	—		—	6/11		—	8/16	—	6/12		—	8/14		—	9/17
Symbol Digit written	18	7		11	16		26	12	4	3		32	33		20	22
Symbol Digit oral	30	0		19	15		22	4	7	2		31	44		26	25
Peabody Raw Score		110		—	90		62	67	—	90		78	87		89	88
SDSS (Face-Hand)	N	L		B	B		B	R	B	B		N	—		N	N
Memory Unrel. Sent.	—	—		—	28		—	12	—	12		—	21		—	23
Hand/eye	R/R	R/R		R/R	R/R		R/R	R/R	R/R	R/L		R/R	R/R		R/L	R/L
Age/sex	29-5/F	31-2		17-10/M	26-1		17-6/M	24-2	28-9/M	37-1		27/F	33-8		25/M	31-10
Education	14			Sp 11	Sp 12		Sp		Sp			10			9	
Test date	23/9/67	23/5/69	28/9/64	19/9/67	5/1/76	9/2/65	27/5/69	2/1/76	17/9/67	3/1/76	11/12/68	24/5/69	3/1/76	10/6/68	23/5/69	3/1/76
Years post-op.		1-7		2-11	11-2		4-2	10-10	1-6	9-10		0-4	7-0		0-10	7-6

Underscored figs. = subnormal. [1] = WISC administered. [2] = Wechsler-Bellevue administered. [3] = Died before second post-op. test. [4] = Not available for second post-op. test. [5] = Prorated. * Subnormal when performance of preferred hand exceeds nonpreferred hand by five or more points.

Comparisons of Pre-operative and Post-operative Wechsler IQs of 4 Patients with Right Hemisphere Structural Lesions

One of the important associated factors was the presence of structural lesions of the right hemisphere pre-operatively in 4 patients (Group RHS). These patients (J.M., N.G., W.J. and M.K.) had complete commissurotomies. Comparisons of their mean Verbal IQ before operation and from fifteen to sixty-seven months after operation show almost identical levels (96.3 and 94.8, respectively) with only negligible individual changes in each of the 4 patients. However, in contrast to the apparent lack of any appreciable effects of commissurotomy on Verbal IQs, comparisons of their mean Performance IQ before (89.3) and after operation (70.5) *reveal a mean decline of 18.8 points, with losses by all 4 patients ranging from ten to twenty-eight points.* While losses in the five individual performance subtests varied, the most marked and consistent declines were in the Block Design subtest. Despite the presence of a long-standing structural lesion in the right hemisphere *before operation*, comparisons of Wechsler subtest weighted scores (Smith, 1981*a*) showed normal or even above-normal scores in Block Design for three (M.K., J.M., W.J.) before complete commissurotomy. Initial post-operative Block Design scores, however, revealed profound losses in all 3 patients with pre-operative structural lesions in the right hemisphere. With respect to the fourth RHS patient (N.G.), the Block Design weighted score (3) was profoundly subnormal even before operation. However, the ten-point drop in N.G.'s Performance IQ four years after operation reflected significant declines among the remaining four performance subtests.

Neuropsychological Test Performances Before and Nineteen Months After Complete Commissurotomy

M.K. was tested with the Michigan Battery before operation. In contrast to the twenty-eight point drop in Performance IQ (88 to 60), the slight decline in Verbal IQ (89 to 86) indicates relative sparing of verbal cognitive functions, contrasting with marked declines in the nonverbal subtests (Table 2). The greatest declines were in Block Design (11 to 3), Object Assembly (10 to 2), and Digit Symbol (5 to 2). Consistent with the marked declines in Block Design, Object Assembly and Digit Symbol, post-operative scores revealed similar declines in the Visual Retention Test (10 to 1), Design Copying (10 to 7), Visual Organization Test (26 to 18), Raven's Coloured Progressive Matrices (34 to 18) and Symbol Digit Modalities Tests with written (18 to 7) and oral (30 to 0) substitutions.

Consistent with other evidence for sparing of verbal cognitive functions, the post-operative Peabody Picture Vocabulary raw score (110) was within the normal range. M.K., with predominantly right hemisphere involvement (including a structural lesion), showed normal pre-operative and post-operative scores in the Digit Span subtest, indicating that immediate auditory memory had not been affected before or after complete commissurotomy.

Initial and Long-term Post-operative Neuropsychological Test Performances of Patients with Complete Commissurotomy and Frontal Commissurotomy

The most consistent deficits in both initial and long-term post-operative tests were shown in written and oral Symbol Digit substitutions. All 10 patients with complete commissurotomy and the 2 with frontal commissurotomy showed markedly subnormal scores in both written and oral Symbol Digit Modalities Tests. Comparisons of Wechsler Digit Symbol substitutions (which are written) showed subnormal scores in pre-operative studies, as well as further declines from the pre-operative subnormal levels. In contrast to other tests described below, these substitution tests revealed no systematic relationship between the side and nature of extra-callosal damage. Post-operative tests of immediate auditory and visual memory variously reflected the side of predominant extra-callosal damage before operation. Comparisons of initial and long-term post-operative Visual Retention Test performances revealed moderate to profound impairment in all 12 patients. Except for one patient (L.B.) with recovery of normal performance, long-term follow-up studies revealed persistent impairment in the Visual Retention Test.

All 5 patients with predominantly right-sided involvement who were tested for Memory of Unrelated Sentences had normal scores. In contrast, long-term post-operative tests of immediate auditory memory for semantic material, as measured by Memory of Unrelated Sentences, revealed greater impairment for those with predominantly left-sided involvement; only one had a normal score for Memory of Unrelated Sentences. Consistent with this, long-term post-operative Peabody Picture Vocabulary Test scores also revealed markedly lower scores by the 5 patients with greater left hemisphere involvement (range 67 to 90, mean 84.4) with no overlapping of scores when compared to the 5 with predominantly right-sided extra-callosal damage (range 92 to 135, mean 113).

While the primary focus of this report is on the effects of frontal and complete commissurotomy on cognitive or 'higher' level cerebral functions, performances on Single and Double (face-hand) Stimulation Tests of somatosensory functions and Purdue Tests of manual motor functions revealed certain effects of commissurotomy on these 'lower' level cerebral functions.

Single and Double Stimulation Tests were administered to 11 of the 12 patients in initial post-operative tests and to 7 in long-term follow-up studies. Initial post-operative tests revealed bilateral deficits in all 9 patients with complete commissurotomy, but normal performances after frontal commissurotomy in 2 patients, despite the left hemisphere complication in N.F. shortly after operation. Long-term post-operative tests showed continuing normal performance by one with frontal commissurotomy and bilateral deficits in 5 of the 7 with complete commissurotomy. In contrast to bilateral Single and Double Stimulation deficits in initial post-operative tests, L.B. showed no errors when retested after an interval of eight years and four months; and C.C. showed only right-sided deficits when retested after an interval of six years and eight months.

Purdue Manual Dexterity Tests of all 12 patients in initial post-operative studies, and 8 of these after a seven to nine year re-test interval, revealed no apparent differences between effects of complete and frontal commissurotomy. Instead, patterns of subnormal manual performance generally corresponded with the reported pattern of greater left or right hemisphere extra-callosal damage before surgery. Retests after a seven- to nine-year interval showed various changes. The most marked change was shown by N.W. Initial tests two years and five months post-operatively revealed normal right-hand performances but markedly subnormal performances with the left. On retest nine years and ten months post-operatively, however, her performances with the left as well as right hand were normal. Purdue Tests using both hands *simultaneously* were introduced in long-term studies. Of 10 patients tested, 4 with complete commissurotomy showed scores within the normal range.

DISCUSSION

The original purpose of this study was to document initial and long-term neuropsychological sequelæ of commissurotomy with a view to evaluating the nature and degree of 'cognitive costs' of commissurotomy for the relief of intractable seizures. Perhaps of greater importance, these data also provide evidence of the principles underlying the organization, disorganization and reorganization of cerebral functions. They also cast light on the specific tests employed.

Both written and oral Symbol Digit Modalities Tests administered to all 12 patients in initial post-operative studies showed markedly subnormal performances, with no improvement in the long-term post-operative tests of 10 patients. Consistent with the view that these substitution tests reflect bilateral processing (Smith, 1973), there were no systematic differences between right *versus* left hemisphere groups.

The second most striking finding in the study is the marked, persisting impairment of nonverbal cognitive functions and the relative sparing of verbal cognitive functions in the 4 patients with established pre-operative right hemisphere lesions (the right hemisphere structural group); the largest declines were in the Block Design subtest.

In terms of the practical clinical implications with respect to 'cognitive costs' of commissurotomy, the findings in this study differ from findings in the patients with callosotomy that led LeDoux *et al.* (1977) to conclude that verbal or nonverbal cognitive functioning 'is largely an intrahemispheric process'.

Comparisons of Wechsler tests before and after frontal or complete commissurotomy show appreciable and persisting impairments; moreover, the impairments are not random. The impairment in nonverbal functions in all patients with pre-operative right hemisphere lesions suggests that these specific post-operative deficits were related to the presence of structural lesions in the right hemisphere *before* complete commissurotomy.

The clearest selective deficit in nonverbal cognitive functions was documented by the pre-operative and nineteen-month post-operative neuropsychological test performances of M.K. In addition to the marked (28 point) decline in the WAIS Performance IQ, reflecting losses in all five performance subtests, the Michigan Battery revealed impairments in other similar tests, including Visual Retention, Raven Coloured Matrices, Visual Organisation and Symbol Digit Modalities Tests. In contrast were her normal performances on tests of language and verbal functions (Peabody Picture Vocabulary and Verbal IQ).

The Visual Retention Test was also administered before and after operation (frontal commissurotomy) to D.M. Although not as marked as the decline in M.K. (10 to 1), the Visual Retention Test score in D.M. declined from a normal level (8) before, to the very defective range (4) ten months after frontal commissurotomy, and improved to the borderline range (6), seven and one-half years post-operatively. Pre-operative scores for the remaining 10 patients were not available. It is interesting to note, however, that the only other patient with frontal commissurotomy (N.F.) showed a similar pattern of improvement in long-term post-operative score (4 to 6). Except for L.B., the remaining 9 patients with complete commissurotomy showed variously subnormal scores with random gains or losses on repeated testing.

In contrast to other measures described below, there was no apparent correlation between the side of greater extra-callosal damage and post-operative performances. The limited improvement and persisting subnormal VRT performances over seven years after frontal commissurotomy indicate that normal maintenance of abilities in this specific visual memory test utilizes structures within both cerebral hemispheres. Moreover, they also suggest that the fibres of the splenium alone are not sufficient to permit maintenance of normal VRT performances in these patients.

Unlike the VRT, performances in tests of Memory for Unrelated Sentences in long-term post-operative studies strongly suggest lateralization differences. Post-operative MUS tests revealed marked to moderate impairment in 4 of the 5 patients with reported greater damage in the left hemisphere *versus* normal scores in all 5 patients with greater damage in the right hemisphere. Consistent with the findings in the MUS test, long-term Peabody Picture Vocabulary performances also indicated lateralization differences. In contrast to the subnormal PPVT scores of all 5 patients with greater damage in the left hemisphere, the long-term post-operative scores of all 5 patients with greater damage in the right hemisphere exceeded the highest score of the comparison group.

In contrast to error-less performances before surgery, Single and Double Simultaneous Face-Hand tests nineteen months after complete commissurotomy in M.K. revealed the emergence of left-sided somatosensory deficits. Since pre-operative structural damage in the right hemisphere was abundantly documented, the absence of left-sided somatosensory deficits in pre-operative tests suggests that the initial deficits were compensated, and that the division of the forebrain commissures disrupted a compensatory reorganization of interhemispheric mechanisms.

It is important to note that the SDSS test of somatosensory functions was the only measure in the Michigan Battery to demonstrate a significant difference between the effects of complete and frontal commissurotomy in initial post-operative studies. Nine patients with complete commissurotomy showed bilateral SDSS errors of extinction and/or displacement. In contrast, the 2 patients with frontal commissurotomy showed normal SDSS performances. The preservation of SDSS in both cases with frontal commissurotomy indicates that a considerable proportion of the interhemispheric links can be sacrificed without permanent disruption of the specific somatosensory functions involved. It is also important to note that the initial post-operative Purdue tests of manual dexterity provided a sensitive and accurate index of the laterality of extra-callosal involvement (*see* Table 1). Purdue performances showed consistent associations of greater impairment in the hand contralateral to the more damaged hemisphere.

Theoretical Implications

First, our findings emphasize the importance of careful documentation of the status of *each* of the two cerebral hemispheres *before* as well as after operation. Our findings are only partly consistent with earlier observations that severe and prolonged seizures often cause bilateral brain damage even in cases where only one hemisphere was originally damaged (Brandt, 1962). The same Michigan Battery (MNTB) administered to 36 cases with left and 28 with right hemispherectomy for intractable seizures revealed ipsilateral sensory and/or motor deficits indicating damage to the residual, presumably intact hemisphere in 32 (89 per cent) with left and 21 (75 per cent) with right hemispherectomy, supporting earlier similar findings (Smith and Sugar, 1975).

This study also contributes toward elucidation of principles underlying the reorganization of human brain functions. Many previous studies of children with extensive, early lesions in the left hemisphere have demonstrated reorganization of compensatory language mechanisms involving the right hemisphere. The question arises as to the converse, following right hemisphere lesions. Namely, does the left hemisphere play a similar role in reorganizing compensatory mechanisms for nonverbal cognitive functions?

As noted above, normal scores in pre-operative tests of constructional functions by patients with right hemisphere lesions might mean that these lesions did not affect the specific functions involved. However, the consistent, marked constructional dyspraxias post-operatively suggest that the normal pre-operative constructional test scores reflect recovery from earlier impairment as a result of the reorganization of compensatory mechanisms. The profound impairment in constructional functions unique to the 4 patients with right hemisphere lesions following complete commissurotomy favours the view that the compensatory mechanisms reorganized for this function were interhemispheric.

Experimental studies of these commissurotomy patients have suggested that the right hemisphere is 'silent' or 'speechless'. However, as Smith (1966, 1969, 1972, 1975, 1978) has frequently reported, studies of adults with left 'dominant' hemispherectomy for tumour have demonstrated not only relative sparing of comprehension, but also a speech performance far superior to that reported for the right hemisphere after complete commissurotomy. Thus, if the right hemisphere in commissurotomy patients seems speechless, this difference may conceivably depend upon downstream left hemisphere influences on the pontine nuclei; or speech capacities may be affected by the initial epileptogenic lesions. In any event, the reported lack of right hemisphere speech following complete commissurotomy need not reflect the maximum capacities of the intact right hemisphere in normal adults (Gazzaniga *et al.*, 1979).

Broca (1865) attributed recovery of speech following left hemisphere damage to the reorganization of cerebral mechanisms involving the third *right* frontal convolution. The significant role of the right hemisphere in the restitution of language functions in most such cases has been abundantly reported by many authors. However, as Goldstein (1948) pointed out, the intactness of the fibres connecting the two hemispheres, and especially the corpus callosum, is important for recovery of language functions. We take particular note of the reports of Russell and Espir (1961) and Russell (1963). Based on detailed anatomical studies of 255 aphasics with penetrating brain wounds, they reported that the undamaged right hemisphere plays an important role in recovery from missile wounds in the left hemisphere, provided that the forebrain commissures are intact. They noted that such recovery did not occur in aphasics with wounds affecting the principal commissures (especially the splenium of the corpus callosum) even though the right hemisphere was intact.

As mentioned above, a major finding in this study is the marked decline in nonverbal cognitive functions and the relative sparing of verbal cognitive functions after complete commissurotomy in the four patients with demonstrated right hemisphere lesions. The striking similarity between the effects of *right* hemispherectomy on performance in the Michigan tests (Smith, 1969, 1972), and of complete commissurotomy in these four patients is noteworthy. In comparisons of the effects of right and left hemispherectomy for glioma in adults, Burklund and Smith (1977) noted that in contrast to the continuing recovery of language functions after left hemispherectomy until recurrence of the tumour, studies of five adults from one to thirty years after right hemispherectomy revealed persisting impairment of nonverbal cognitive functions. This difference in the patterns of recovery suggested that residual structures after left 'dominant' hemispherectomy compensate for the loss of language functions to a greater degree than the residual structures following right hemispherectomy can compensate for the loss of nonverbal cognitive functions.

The significantly higher levels of nonverbal cognitive functions before disconnection of the two cerebral hemispheres in these four patients suggests that following damage to the right hemisphere, the forebrain commissures contribute to a reorganization of interhemispheric relations to permit restitution of the diminished nonverbal cognitive functions resulting from right hemisphere damage. Thus, our findings indicate that in addition to other possible roles in integrating the functions of the two cerebral hemispheres in the normal brain, the forebrain commissures can also serve as 'standby' or 'reserve' structures for reorganization of compensatory mechanisms following lateralized brain insults.

In view of the continued improvement in some of these patients, definition of the extent of ultimate competence requires continuing long-term follow-up studies. Apart from their practical clinical implications, such studies may also contribute to the elucidation of the principles underlying the organization, disorganization and reorganization of human brain functions.

SUMMARY

Neuropsychological studies of 10 patients with complete cerebral commissurotomy and 2 with frontal commissurotomy showed differences in the nature and severity of pre-operative, initial and long-term post-operative deficits in verbal and nonverbal cognitive, memory, and sensorimotor functions. Neurosurgical findings before and after operation recorded various types of extra-callosal brain damage in all 12 patients, including 4 with gross structural lesions in the right hemisphere before surgery. Our findings revealed that differences in the nature and severity of pre-operative and post-operative deficits varied according to the nature and laterality of associated extra-callosal damage *before* as well as after operation.

Following complete commissurotomy, all 4 patients with pre-operative structural lesions of the right hemisphere revealed a unique pattern of marked, selective impairment of nonverbal cognitive functions strikingly similar to the effects of right hemispherectomy for tumour in adults. The remaining 8 patients showed systematic patterns of greater impairment in verbal or nonverbal cognitive and contralateral sensorimotor functions, depending on the laterality of extra-callosal damage.

The significantly higher pre-operative Wechsler Performance IQs of the 4 patients with structural lesions of the right hemisphere suggest that following earlier damage to the right hemisphere, the forebrain commissures contribute to a reorganization of interhemispheric relations to permit restitution of the diminished nonverbal cognitive functions resulting from damage to the right hemisphere. Thus, in addition to other possible roles in integrating the functions of the two hemispheres in the normal brain, the forebrain commissures can also serve as 'standby' or 'reserve' structures for reorganization of compensatory interhemispheric mechanisms following lateralized brain insults. Since some patients showed later post-operative improvement, the extent of ultimate competence and the 'cognitive costs'

of commissurotomy can only be defined by continuing follow-up studies. Apart from their practical clinical implications, such studies may also contribute to elucidation of the principles underlying the organization, disorganization and reorganization of human brain functions.

ACKNOWLEDGEMENTS

This work was partially supported by NINCDS Grant No. 2R01-NS10089 to Professor Aaron Smith and No. SF32-NS05575 to Dr A. L. Campbell, Jr. We thank Dr Jeffrey Schaeffer for assistance in testing some of these patients.

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(*Received August 12, 1980*)

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HUMAN POSTURAL RESPONSES

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INTRODUCTION

IN previous papers we have described servo action in various muscles used as prime movers in voluntary tasks. In those experiments we usually took pains to isolate the movement being studied by applying clamps to other parts of the limb, steadying joints, etc. (Marsden, Merton and Morton, 1972, 1976*a*, *b*). In ordinary life, with a free-moving unsupported subject without such restraints, servo compensation in the prime movers will be ineffective at dealing with perturbations applied to a moving extremity unless the trunk and the other parts of the active limb are prevented, by appropriate postural contractions, from swaying or otherwise yielding. Postural responses of this and related kinds are described and investigated in the present paper. They are easily found in electromyographic recordings. Their striking feature is their short latency: of the order of a fifteenth of a second. In this and other ways they are superficially very similar to the servo responses in the prime mover, but their genesis proves, in general, to be quite different—as we go to some lengths to show. Preliminary accounts of some of these experiments have been given (Marsden *et al.*, 1976*c*, 1978).

METHODS

The general arrangements for studying responses to unexpected perturbations in the course of a voluntary movement have been described in earlier papers (Marsden *et al.*, 1976*a*, *b*). Briefly, a low-inertia electric motor provided both the initial force against which a movement began and the subsequent perturbations that were introduced randomly in its course. The rate of each movement was paced by a visual tracking task. The usual set of four superimposed responses, the recorded averages of the integrated electromyogram of the active muscle, to stretch, to release and to halting during a movement, together with the average of control trials, is referred to as a 'tulip'. In the present experiments the pull from the electric motor was taken by a flexible steel wire looped around the pad of the thumb or the wrist, or connected to a harness around the subject's hips. The wire was wound on a drum on the motor shaft and its movements were recorded by a potentiometer in terms of angular displacement of the shaft. The initial force in this wire was always 300 g (2.9 N), it rose to 570 g (5.6 N) during a stretch trial and fell to 120 g (1.2 N) during a release. Compared with what the arms and trunk often have to deal with, the present forces are all very moderate.

Pairs of surface electrodes were used, usually 4 cm apart, lying longitudinally on the muscle under observation. They were either silver cups stuck on with surgical tape and filled with jelly, or gauze-covered pad electrodes wetted with saline. In the order in which the muscles appear in the text the placements were: for flexor pollicis longus, over the muscle, 8 and 12 cm above the wrist crease; for pectoralis major, 10 cm lateral to the manubrium; for tensor fasciæ latæ, 6 and 10 cm below the crest of the ilium; for flexor hallucis longus, one electrode 3 cm behind and 3 cm above the medial malleolus, the other 6 cm above the lateral malleolus, behind the fibula; for the ankle extensors (triceps suræ), over the middle of the calf, half way between knee and ankle; for erector spinæ, over the left muscle, opposite the second lumbar spine; for quadriceps over the front of the thigh, midway between hip and knee; for hamstrings, similarly, but over the back of the thigh; for biceps brachii, over the belly of the muscle; for triceps, 8 and 12 cm above the condyles.

Swaying of the trunk and other parts was measured with a differential photocell (United Detector Technology Inc., type PIN-SC/25). The light from a 6-V pea-bulb attached to the subject was focused by a 35 mm camera lens, some 30 cm distant, on to the photocell. After a direct-coupled first stage, condenser-coupled amplification was used, with a time constant of either 0.05 s or 1 s. So that each record started from the same level, the condenser input to the main amplifier was clamped to zero and released at the start of the sweep. There was a meter across the output of the preamplifier which the subject kept an eye on to make sure that the preamplifier was near the middle of its range and not overloading. If it was, he moved position suitably. The instrument was calibrated with direct-coupled amplification at a known lower gain setting and without the clamp.

In one of the experiments with the pull of the wire loop taken on the wrist, it was desired to know the effective mass presented to the wire. This was mainly in the forearm and hand and was estimated as follows: the wrist was slung from a spring balance, with the sling around the same place as the wire loop occupied in an experiment. With the forearm horizontal and the elbow muscles relaxed the apparent weight recorded by the spring balance gives the effective mass for other accelerative forces.

The subjects were two of the authors, P.A.M. and C.D.M.

RESULTS

Pectoralis Major

We start from the observation illustrated in fig. 10C of Marsden *et al.* (1976*b*) and repeated with modifications for this paper. The subject stands without support. The thumb of the pendant left arm, its movement resisted by the pull of a wire looped round the distal phalanx, smoothly pulls on the wire from left to right, towards the side of the trunk. The wire runs to a winch drum on an electric motor away from the subject to his left. When the movements are interfered with, by applying perturbations through the electric motor that tensions the wire, sets of compensatory responses in the muscles, which we have called 'tulips' (*see* Methods) can be recorded simultaneously from the long flexor of the thumb (fig. 1D) and from pectoralis major—the muscle acting on the shoulder joint that pulls the arm towards the side of the trunk and opposes the pull of the wire (fig. 1C). The tulips in the two muscles are in the same sense, for example, an unexpected increase in tension in the wire (a stretch trial) causes an increase in the contraction of both muscles. Thus the response in pectoralis will tend to back up the reflex thumb flexion that opposes the perturbation, by preventing the arm from being pulled away from the subject's side. The reverse occurs with a release response in the thumb flexor. In general, the responses represented in the pectoralis tulip can be regarded as reinforcing the posture of the arm, so that the long thumb flexor can exercise its well-known servo-like properties to react to imposed perturbations.

The tulip in pectoralis in fig. 1c appears to differ in its mechanism from the tulip in the thumb muscle and is not caused, so far as we can tell, by reflexes arising from receptors in or near pectoralis itself. A strong indication of this was obtained by recording the displacement of the upper arm, using a pea-bulb taped to the medial

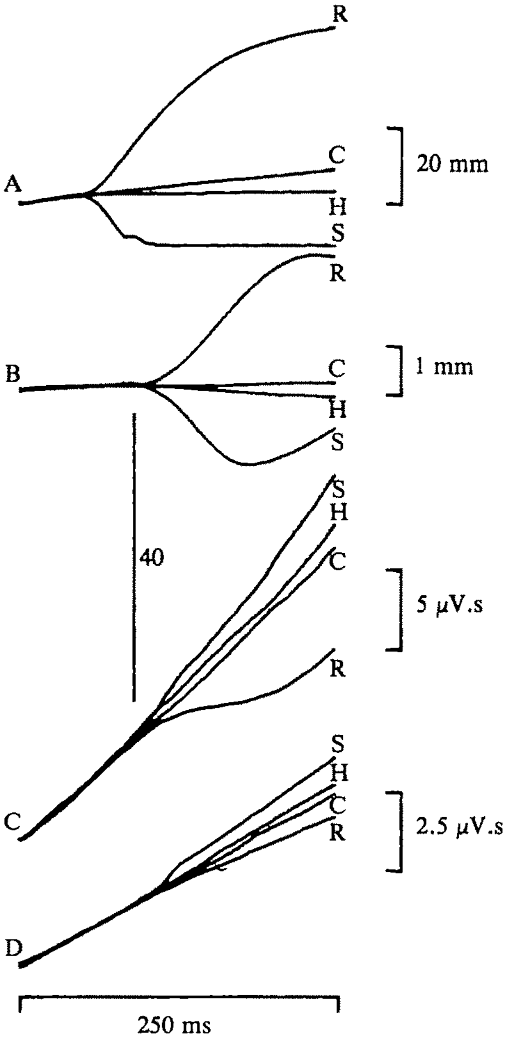

FIG. 1. An experiment recording simultaneous 'tulip' responses in the integrated electromyogram from D, flexor pollicis longus and C, pectoralis major, during adduction of the arm. A, the corresponding records of linear displacement of the thumb. B, records made photoelectrically at the same time of the movement of the left elbow; the trace moves downwards for movements towards the motor. The four modes are labelled: C, control; H, halt; R, release; S, stretch. The timing line is at 40 ms after the time of the imposition of perturbations. Each trace is the average of 32. June 26, 1979.

epicondyle of the humerus and the sensitive photoelectric detector described in Methods. (This was not done in the otherwise similar experiments published in 1976.) The records obtained (fig. 1B) show that there was no definite movement of the upper arm until about 45 ms after perturbations were applied to the thumb, by which time the tulip in pectoralis had already started. So it seemed improbable that movements of the upper arm could reflexly elicit the tulip in pectoralis by stretching the muscle or allowing it to shorten, because the tulip started before the bone acting on the muscle could be shown to move.

On the other hand it was shown in the earlier paper that tulips in pectoralis major could be obtained by applying perturbations directly to the elbow or to the wrist. In these instances, however, there is no need to doubt that the responses seen are reflexes set up in pectoralis itself, for we have found that the upper arm starts to move earlier with these arrangements and the responses in pectoralis are later than with the pull taken on the thumb (not illustrated). In addition, it has been shown (Marsden *et al.*, 1977, fig. 8) that tulips with the pull at the elbow are convincingly unaffected by anæsthetizing the arm with a blood-pressure cuff up to the axilla; and this has been confirmed for responses with the pull at the wrist in the present experiments. So the receptors responsible must lie round the shoulder, presumably in pectoralis.

It would thus seem that there can be two kinds of tulips in pectoralis: the familiar kind due to reflex responses from the muscle itself, seen when perturbations are applied to the wrist and the elbow, and another kind, seen when the pull is taken on the thumb and not based on the stretch reflex in pectoralis or, for that matter, on any other reflex caused by movement above the elbow. The latter is probably caused by afferent signals from the long thumb flexor. Hence we distinguish autogenetic reflex tulips in prime-moving muscles (here flexor pollicis longus) and in other muscles, based on the stretch reflex in those muscles, from heterogenetically-driven tulips in postural muscles (here pectoralis major), driven from receptors not in those muscles; or more briefly '*reflex*' from '*driven*' tulips. (Strictly, driven tulips are also reflex—by an indirect route; but the above is a useful shorthand.)

Tensor Fasciæ Latæ

The success with pectoralis major led us to look further afield for postural tulips. The first muscle tried was tensor fasciæ latæ. The experiment differs from the experiments on pectoralis only in having an extra recording channel for the electromyogram of tensor fasciæ latæ. If the subject's stance is adjusted carefully so that, when he pulls on the wire with his left thumb, the tensor fasciæ latæ muscle on the same side of the body as the arm in use is called mildly into play, a tulip can be recorded from this muscle too at a latency of 65 ms. This is illustrated in fig. 2A–D. In this task a stretch perturbation applied to the thumb will, *via* the arm, tend to pull the subject's trunk and pelvis to the left, towards the wire and the motor, and this from the geometry would stretch the left tensor fasciæ latæ. The response observed in tensor fasciæ latæ is an increase of activity, that is, it is in the correct sense to oppose the sway of the subject's body caused by the perturbation (fig. 2C). The same is true of the other perturbations. Thus reactions to maintain posture occur not only in the limb itself, but also in distant muscles of the hip and trunk.

Tensor fasciæ latæ tulips are presumably 'driven', because the movement of the pelvis in the latent period preceding postural tulips in tensor fasciæ latæ is extremely

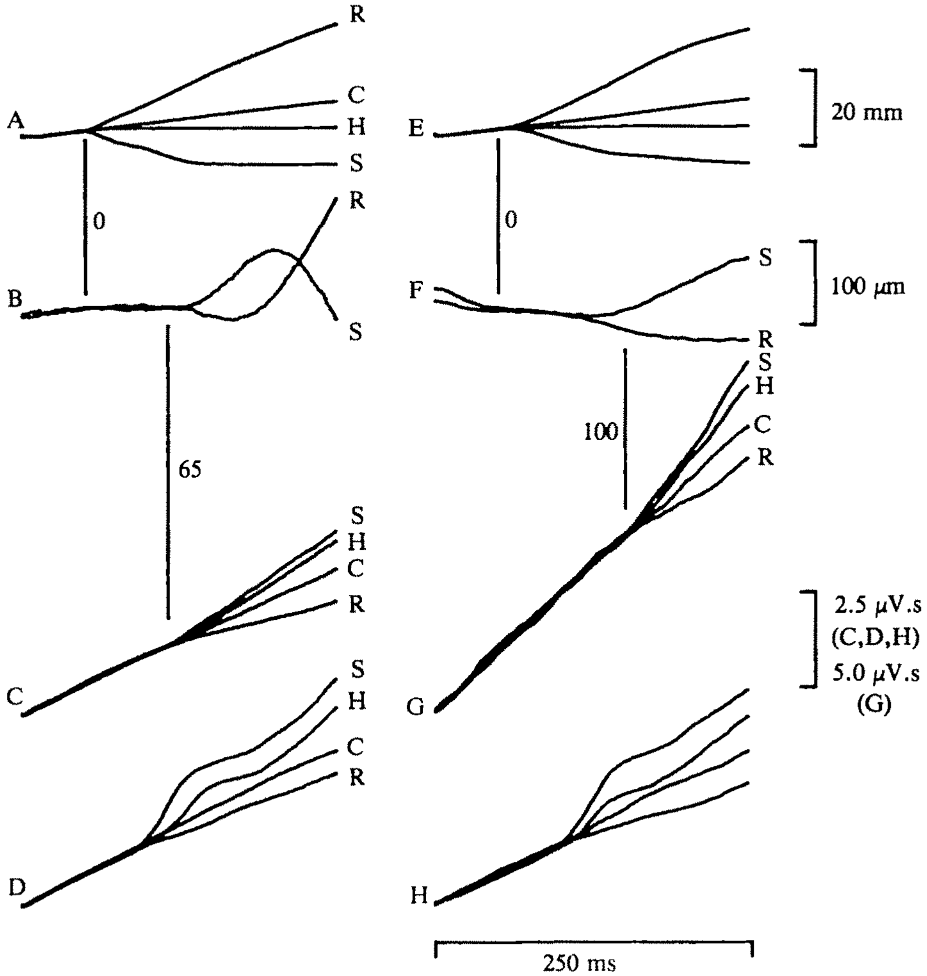

FIG. 2. Postural responses in tensor fasciæ latæ and in flexor hallucis longus, with body sway monitored. In both cases the subject pulled on the wire from the motor with his left thumb; there were controls and the usual three perturbations. A–D, simultaneous tulips recorded in tensor fasciæ latæ (C) and flexor pollicis longus (D) together with records of thumb displacement (A) and lateral displacement of the hip (B). For the photoelectric records in B, only the S and R traces are plotted; sway of the trunk towards the motor moves the trace downwards, so the first detectable movement in the stretch trials is away from the motor. Timing lines at the imposition of perturbations and 65 ms later. Each trace is the average of 64. November 21, 1976. E–H, a similar experiment on flexor hallucis longus (G) and flexor pollicis longus (H), showing the longer latency, of 100 ms, of the postural tulip (G). The record of antero-posterior movement of the pelvis (F) moves in the same sense as in B and thus shows a movement away from the motor after a stretch to the thumb, lasting to the end of the sweep. Each trace is the average of 32. December 5, 1976.

small. This is to be expected. The extra force applied to the wire in a stretch trial is only 270 g (*see* Methods) or 0.4 per cent of the weight of a 70 kg man; if this acted at the centre of mass the acceleration would be 0.4 per cent of *g* and the movement resulting only 8 μm in the first 20 ms. In practice it should be substantially less, for this force (and the smaller change of force in other perturbations) is applied, not directly to the centre of mass, but at the end of a long, compliant limb. Using the sensitive technique for recording displacement described in Methods it was confirmed (fig. 2B) that the movement of the pelvis in the averages of the perturbed trials was well under 10 μm in the first 20 ms after imposition of perturbations, and, indeed, for a considerably longer period. So in the early part of the latent period, when the reflex stimulus that causes the tulip must arise, movement of the pelvis appears insignificant. When it does become manifest, movement is initially, for 50 ms or so, in the reverse direction to that needed to cause the responses by reflex action. This is seen clearly in fig. 2B. In the stretch trials the pelvis only starts moving towards the motor in the last quarter of the sweep; and *vice versa* for release. The initial reverse movement is presumably because perturbations transmitted to the trunk *via* the shoulder cause a small transient swivelling of the trunk about a fore-and-aft axis. Thus trunk movement is apparently too late and, when it comes, is in the wrong direction to cause the postural tulip.

Flexor Hallucis Longus

Encouraged by these experiments with tensor fasciæ latæ, we next attempted to get postural tulips in an even more distant muscle, the long flexor of the great toe. For this experiment the subject stood facing the motor; he was barefooted with most of his weight taken on the left foot, leaning slightly forward so that the pad of the great toe pressed on the ground. His left arm was straight with the hand slightly in front of the left hip and supinated to bring the thumb into a position in which flexion of it pulled on the wire hitched across the terminal phalanx. With this arrangement definite tulips were obtained from electrodes over flexor hallucis longus (fig. 2G) in the same experimental runs with those from flexor pollicis longus (fig. 2H). (Muscles other than flexor hallucis longus, but likely to be of similar action, may have contributed to the responses recorded.)

Body sway was also recorded in these experiments, in this case in the fore-and-aft direction. The records (fig. 2F) were similar to those in the tensor fasciæ latæ experiments in failing to reveal movements of more than a few micrometers in the early part of the latent period after perturbations were imposed. In this case too the initial movements of the pelvis were opposite to the direction of stretch or release of the wire. In fact, in stretch trials the pelvis had not started to move towards the motor by the end of the recording sweep. Once again, then, body sway appears to be at the wrong time and in the wrong sense to cause the postural responses observed. Another fact bearing on the question of whether body sway acting on the long flexor of the toe could cause the postural tulips seen in it is that the latency of these tulips, about 100 ms, is only about 10 ms longer than the latency of the tulips obtained in the same subject when perturbations were applied directly to the big toe (Marsden *et al.*, 1976*b*, fig. 6A). With perturbations applied as far away as the thumb one might expect mechanically induced lags of much longer than 10 ms to intrude, as, indeed, the recordings of body sway show that they do.

Back and Thigh Muscles

Traub, Rothwell and Marsden (1980) have found, and we have confirmed, that responses, similar to those in flexor hallucis longus, can easily be recorded over the ankle extensors, gastrocnemius and soleus (triceps suræ). This particular postural tulip has been adopted in the systematic investigation of patients. We have also looked at postural responses in other large commonplace postural muscles. For these experiments the subject knelt in front of the motor. The wire loop was around the left wrist (protected by sticking plaster) and the subject pulled on it by flexing his elbow, which was approximately at a right angle. No part of the subject above the knees touched anything; so any reaction to forces in the wire tending to make the body sway depended ultimately on the muscles flexing or extending the knees. Simultaneous recordings were made from electrodes over the left erector spinæ, left quadriceps and left hamstrings. The results are shown in fig. 3. Tulips were obtained from all three muscles, that in quadriceps being inverted, as it ought to be (for example, a stretch applied to the wrist should tend to relax quadriceps). The latencies were 65 ms for erector spinæ, 75 ms for quadriceps and 100 ms for hamstrings (but *see below*). In this experiment it proved difficult for the subject to find a stance in which all three muscles simultaneously produced full tulips. If the top half of the body leant too far back on the pelvis, the erector spinæ gave a good response to a release at the wrist, but little from a stretch or a halt. If the whole body leant too far back, the hamstrings relaxed and only a late response to stretch and little else could be obtained from them, as in fig. 3B. A full hamstrings tulip from another run, with a latency of 65 ms, is given in fig. 3D. Body sway was not monitored in these experiments.

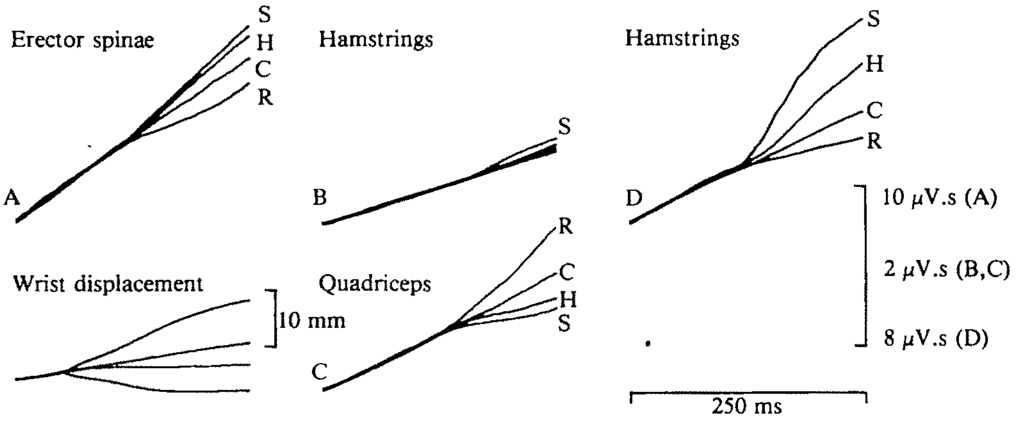

FIG. 3. Postural tulips in erector spinæ, quadriceps femoris and hamstrings during flexion movements of the elbow, with the wire round the left wrist, and the usual task. The subject was kneeling. The four records on the left were made simultaneously and show postural tulips in the three muscle groups, and left wrist displacement. The better hamstring tulip on the right was from another similar experiment with the subject leaning more forwards. Each trace is the average of 32. December 10, 1976 and January 16, 1977.

Although the procedure proved unpleasant, it was thought worthwhile to see whether anæsthesia of the lower legs had any effect on thigh or back tulips. In an experiment otherwise the same as that just described cuffs were applied above both knees to occlude the circulation for about 1¼ hours. By that time the legs, including the knee joints, were anæsthetic at least up to the lower level of the cuffs. Postural tulips from quadriceps, hamstrings and erector spinæ were apparently unchanged, as compared with controls done before starting occlusion.

Biceps and Triceps

With the subject kneeling and the same general arrangements as in the last experiments we also looked to see what happened when the subject used his opposite (right) hand to steady himself, by holding on to the right-hand edge of the table that carried the motor. Records were made from electrodes over the left biceps and over the right biceps and triceps. As expected, when perturbations were applied to the left wrist, the subject used his right biceps and triceps to exert force on the motor table to steady himself. Postural tulips were obtained at the first attempt from both muscles in both subjects, that from the right biceps being inverted, as it ought to be. The same difficulty as before was met with in getting full tulips simultaneously from the pair of antagonistic muscles. In the first column of records in fig. 4, the subject's attitude resulted in a good (inverted) tulip in crossed biceps (fig. 4D) at a latency of about 55 ms. Triceps was almost relaxed and the tulip obtained (fig. 4C) showed big but somewhat hesitant stretch and halt responses and very little to release. Records were also taken from the left biceps, one of the prime-moving muscles. The tulip obtained was small (fig. 4B), probably because a substantial background activity in biceps was continuously required merely to hold up the forearm against gravity at the angle at which it was used (*cf.* fig. 5 for a better tulip in a prime mover). In another experimental run, giving the right-hand column of fig. 4, the triceps was

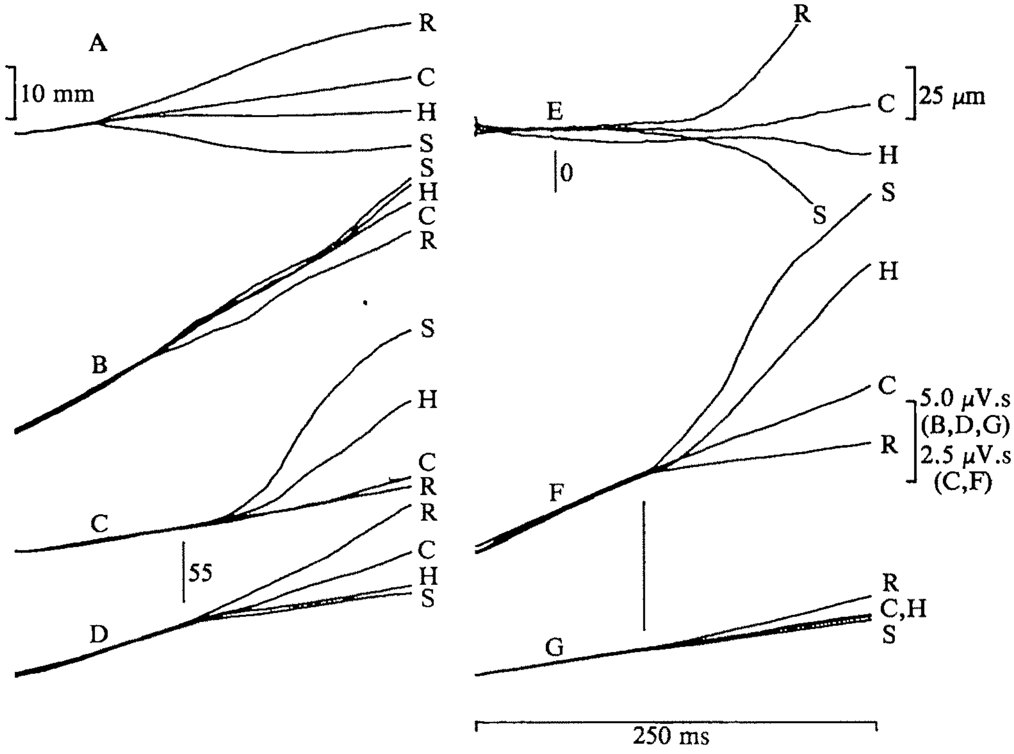

FIG. 4. Postural tulips in triceps and biceps during flexion movements of the opposite elbow. The subject knelt and held the table top with his right hand. He pulled on the wire with his left wrist. A–D, simultaneous records of A, displacement of the left wrist, B, tulip responses in *left* biceps (a prime mover), C and D, postural tulips in *right* triceps and biceps, respectively. Timing line at 55 ms after perturbations start. Each trace is the average of 32. December 11, 1976. E–G, from another similar experiment. F and G, postural tulips in triceps and biceps, respectively. E, displacement of the tip of the right shoulder recorded photoelectrically in the same experimental runs. Movement of the shoulder forwards, towards the motor, moves the trace downwards. Each trace is the average of 64. December 12, 1976.

contracting more than biceps and gave a very large tulip (fig. 4F), with a sharp latency of 55 ms. The release almost silences triceps. The records of left wrist displacement were closely similar to those in the left-hand column and are not plotted; but in this experiment movements of the right shoulder were recorded and plotted. It is seen that during the latent period of the postural tulip in the right triceps, movements of the shoulder above it were very small. Without significant displacement of the shoulder, the elbow joint presumably cannot have been moved and the triceps muscle cannot have changed in length; so once again we appear to be faced, in triceps, with a 'driven' tulip.

Another line of investigation tending to the same conclusion, but of interest on its own account in more ways than one, concerns the sensitivity of the crossed reactions. The postural tulips in triceps diverge as much, that is, show as great a responsiveness as any others so far met with. Clearly they could be elicited by much smaller perturbations. The question is how small. In subject P.A.M. we have, on several occasions, got good responses with 'stretches' and releases applied to the left

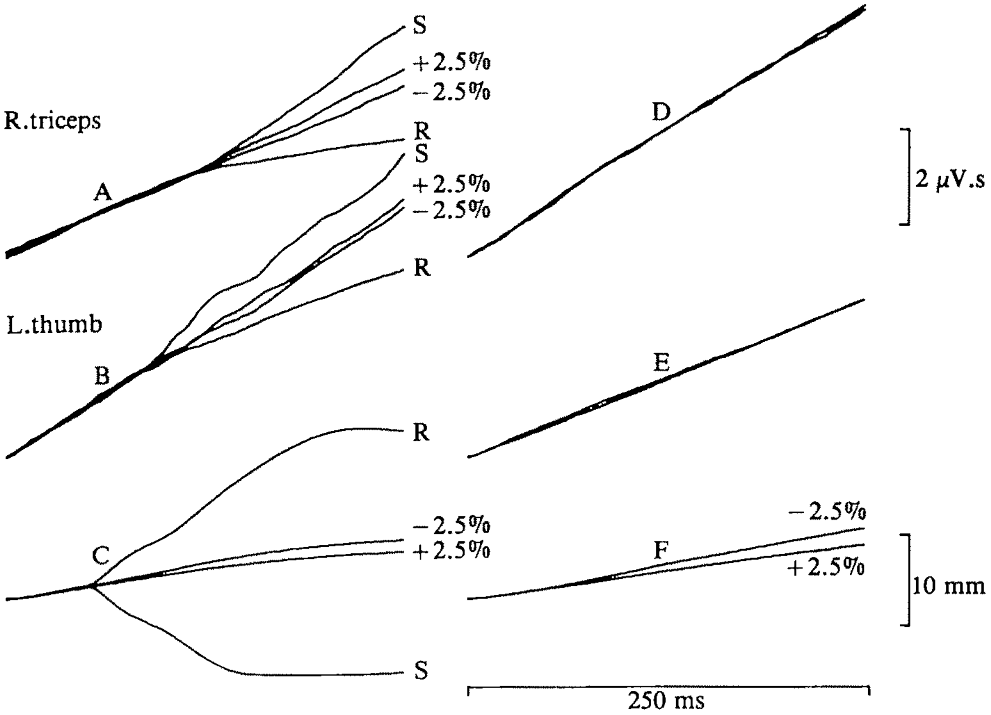

FIG. 5. Postural responses from small perturbations. The arrangements were as for fig. 4, except that the pull of the wire was taken by the pad of the left thumb. A, B and C are simultaneous records of A, postural responses in the opposite (*right*) triceps; B, tulip responses in the left flexor pollicis longus (a prime mover); C, displacement of left thumb. The records for normal stretch and release perturbations are plotted together with those for load changes of ±2.5 per cent. The control records are not plotted. Each trace is the average of 24. January 8, 1978. D, E and F are corresponding records of an experiment in which only controls (not plotted) and ±2.5 per cent perturbations were used, showing that in runs without the ordinary large perturbations there is no response to the small ones. Each trace is the average of 24. January 3, 1978.

wrist or thumb of only ±2.5 per cent of the initial tension in the wire (such a 'stretch' only retards and does not actually reverse motion). To start with, in April and August 1977, such perturbations were effective in experiments in which they were the only perturbations applied, but subsequently in October 1977 and later, following a pattern of behaviour we have come to recognize (Marsden *et al.*, 1979), they produced significant responses only if mixed in, randomly, with large perturbations. Fig. 5A–C gives the results of one such experiment. The pull of the wire was taken round the pad of the left thumb and records were taken over the long flexor. Tulips are shown both in this muscle (fig. 5B) and in the crossed triceps (fig. 5A). There is a clear response to the ±2.5 per cent perturbations in both. Fig. 5D–F is from an experiment on another day; it shows a typical failure of response in both muscles to small perturbations, in the absence of large ones. From this and several other experiments with both ±2.5 per cent and ±5 per cent perturbations, we conclude that the threshold is much the same in both prime mover and postural muscle, that it is very low, but is often only reached if trials with large perturbations are mixed in with the threshold ones. A perturbation of 2.5 per cent with our standard initial force of 300 g is only 7.5 g and it seems most improbable that the effects of such a small force applied to the top of the thumb could be rapidly transmitted mechanically to the opposite triceps. This again reinforces our view that the crossed responses are 'driven'.

For the case with the wire round the wrist an upper limit for the deceleration of the forearm with a +7.5 g perturbation (2.5 per cent) can be estimated. The effective mass of the forearm as seen by the wire at the wrist, measured as described in Methods, was 1.2 kg; 7.5 g is 0.6 per cent of this, giving a deceleration of 0.6 per cent of *g*. If a perturbation has to reach threshold in, say 20 ms, the retardation to be detected would be 12 μm; and this is an upper limit. Perturbations of ±2.5 per cent on the 300 g initial force appeared to the subject to be well below the threshold for conscious appreciation during the tracking task. A few forced-choice threshold determinations which confirmed this impression were made on P.A.M.

Turning attention now to the opposite (right) arm, it was noticed early on that if the subject let go of the table, all responses vanished. This and various other observations (*see* p. 525) suggest that triceps does not respond unless the hand is recognized to be in contact with a firm object, so that postural contractions in triceps can achieve some good. This raises questions about the recognition of firmness. A significant point is that recognition appears to be done at a subconscious level, as was frequently emphasized by the observation that, in any experiment without a loudspeaker on the electromyogram amplifier, the subject has scant notion of whether his triceps is responding or not. To investigate the problem further we attached one end of the handle that the right hand held to a vertical crank on a second electric motor. The opposite end was slung from above so that the handle was horizontal. The motor could either be held stationary by a high-gain positional servo (so that the handle appeared to be fixed) or allowed to turn (so that the handle was floppy). We started out to compare experimental runs in which the handle was fixed throughout, with runs in which the handle became floppy for a second, starting immediately after a perturbation was applied to the opposite wrist. In the left arm the forces and perturbations were the standard ones, as for fig. 4, etc. This experiment badly upset the subconscious motor system. At the start (with the handle fixed throughout) good standard crossed tulips were obtained. A single run with floppy periods caused much attenuation, but on returning to a fixed handle the responses, instead of improving, got still worse. After trying for some time to get the responses back and partially succeeding, it was found that in the aftermath of another 'floppy' run, responses were almost absent even when the subject gripped the edge of the table top in the original manner. After several days of experiments of this kind, attention was given to the legs and some control over the phenomenon achieved. Briefly it was found that the long-lasting decay of the triceps tulip that followed runs with a floppy handle could be reversed by a change of tactics. When the subject knelt before the motor table and held it with his right hand, without giving the matter special thought, it was observed that both his thighs and his right arm naturally tensed slightly to maintain posture. If now by introspection and effort the subject voluntarily relaxed his thighs—both hamstrings and quadriceps—the responsibility for postural stability was thrown more on to the right arm and triceps tulips that had failed reappeared.

In the final experiments it was arranged that when the positional servo on the second motor was electronically switched off, the motor current did not fall to zero, but was held at the final level it had reached when the servo was on. This meant that, with the subject pushing gently on the handle to steady himself, there was no sudden change in the resistance he felt when the motor changed from the 'locked' to the 'unlocked' state. The motor, thus, did not go floppy but offered a constant force to movement of the handle. This avoided sudden movements of the handle, which were thought undesirable. The timing was that the motor became unlocked a second or two before the subject made a trial movement with his left arm. Three seconds after this trial the positional servo was again engaged and the handle, if it had moved, was forcibly returned to its original position. After one second the motor became unlocked again and the subject then made the next movement in his own time, in practice a second or two later, as stated above. In the definitive series, a preliminary run was done with the motor locked by the servo throughout. Then followed a run with the motor unlocking as described; and then there was another run with the motor locked. A sequence of this kind was gone through with the subject paying no particular attention to his legs. After a few minutes rest a similar sequence was carried through with the subject attempting actively to relax his quadriceps and hamstrings and keep his balance with his right arm, which was, of course, holding the handle as before. Then, after another rest, the original sequence was repeated; and so on, until four of each kind of sequence had been recorded. The grand averages are plotted in fig. 6. When no special effort was made to relax the thighs (upper row), fair preliminary tulips were obtained (fig. 6A). With the handle unlocked (fig. 6B) they were much impaired, and were definitely worse again (confirmed on individual sequences) in the final runs of the sequence, with the handle locked (fig. 6C). With the thighs relaxed, both the preliminary and the final tulips (fig. 6D and F) were healthier, almost up to the standard of fig. 4, and they were not much impaired even when the handle was unlocked (fig. 6E). (As the 'unlocked' handle continues to offer a constant resistance, this finding does not necessarily conflict with the earlier result that postural responses disappear with a completely 'floppy' handle.) The effect of relaxing the thighs was seen after only a few minutes interval of rest and it might even be immediate for all we know.

Our conclusions are that loss of firmness in the handle is sensed, if not at once, at any rate within a few trials. It leads to a rapid failure of the crossed triceps tulip,

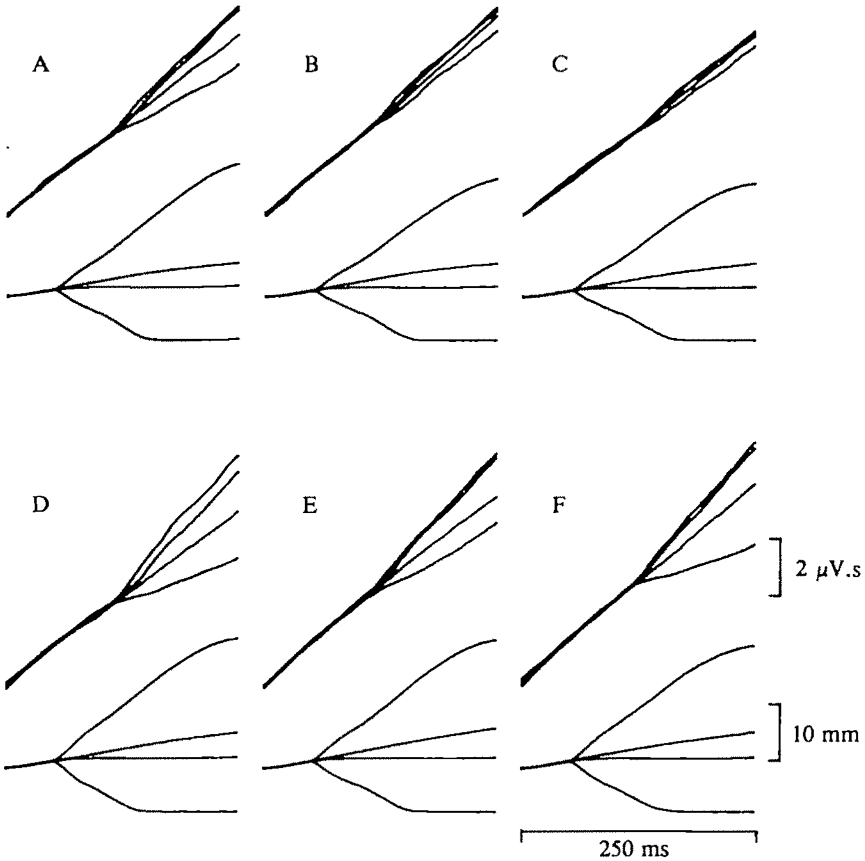

FIG. 6. The effect of a yielding handle on postural tulips in triceps. The arrangements were as for fig. 4, but the right hand gripped a handle which might either be rigid (locked) or be free to move under a constant force (unlocked). A, postural tulip in right triceps with handle locked throughout; records below are displacement of left wrist. B, the same but with the handle unlocked during the movements of the left wrist. C, the same; records made immediately after unlocked runs (B) but with the handle locked throughout as in A, showing further deterioration in the tulip. D, E and F: records made under conditions similar to those in the records (A, B and C) immediately above each pair, but with the subject voluntarily relaxing his thighs, as described in the text. Each trace is the average of 32. January 9, 1978.

which may continue into a further slow decay, even when the handle is made firm again. This state may continue indefinitely, possibly for days, and the subject may be powerless to reverse it. One trick, rapidly successful in one subject, was to relax the thighs to throw the onus for stability on to the arm. In this condition tolerable tulips (fig. 6E) were seen even with the handle unlocked (that is, offering a constant resistance), contradicting the early impression that crossed tulips required a firm handle and offering a striking contrast to the utter inability of the same subject to get a tulip even when holding the table in other circumstances.

Another example of erratic behaviour was seen in C.D.M., the second subject. Like P.A.M., he gave excellent crossed tulips in triceps on the first occasion he tried, and on later occasions. One day, however, nine months after the first session, for no apparent reason he utterly failed to start with, and could not be persuaded to produce more than a minimal tulip all that afternoon, even when he voluntarily relaxed his thighs.

Steadying a Teacup

We have seen what happens when a subject pulling on a wire with his left arm steadies himself by holding on to a table with his other hand, for instance, an unexpected pull on the left arm causes contraction of the right triceps to push against the table and offset the effect of the pull. Suppose now that, instead of holding the table, the subject was holding a cup of tea in his right hand; if the same reaction occurred it would spill the tea; to avoid this the opposite response is required: relaxation of the right triceps and contraction of biceps. The experiment was easily tried.

To begin with, a cup of tea was used, but it was soon abandoned and an essentially similar but experimentally more convenient task substituted. The right wrist was slung from above by a long cord, with the forearm horizontal, so that the subject did not have to hold up his arm for long periods. The tips of the extended fingers pressed lightly on a 500 g weight hung from the frame by a string about 10 cm long. The subject performed the usual task with his left wrist and encountered the usual perturbations. His intention was to keep the pressure on the 500 g weight constant throughout and avoid moving it backwards or forwards (but as we shall see below it is not certain that his immediate intention matters). Some records from triceps were obtained which appeared to start as an ordinary postural tulip and then to reverse. Pure inverted tulips were soon seen, however, as depicted in fig. 7A. They had a latency of some 85 ms, that is, about 30 ms longer than for an ordinary crossed postural tulip in triceps (fig. 7B). It was striking that if the fingertips were moved sideways a few centimetres to touch the solid upright of the frame, ordinary postural responses appeared at once in triceps and could not be suppressed by the subject.

These inverted 'teacup' tulips are believed to be automatic rather than voluntary; 85 ms is improbably short for a voluntary reaction time in a four-choice situation. But perhaps the best evidence of their involuntary nature came by accident. In some later experiments we were endeavouring to find out how 'solid' a solid object had to be to cause the subject to get a postural tulip in triceps when he held on to it to steady himself. One such object was a 5 kg weight slung from above. Quite unexpectedly, when this was gripped, inverted responses were obtained; 5 kg dangling was unconsciously treated by the subject as if it were a teacup. It thus proves, as conjectured, that the crossed arm can make at least two different types of automatic postural response, one when it is in use to steady the body, the other when it is holding a cup of tea or some such object; and that the choice between the possible reactions (which may or may not agree with the subject's conscious notions of what is appropriate) is also made at a subconscious level.

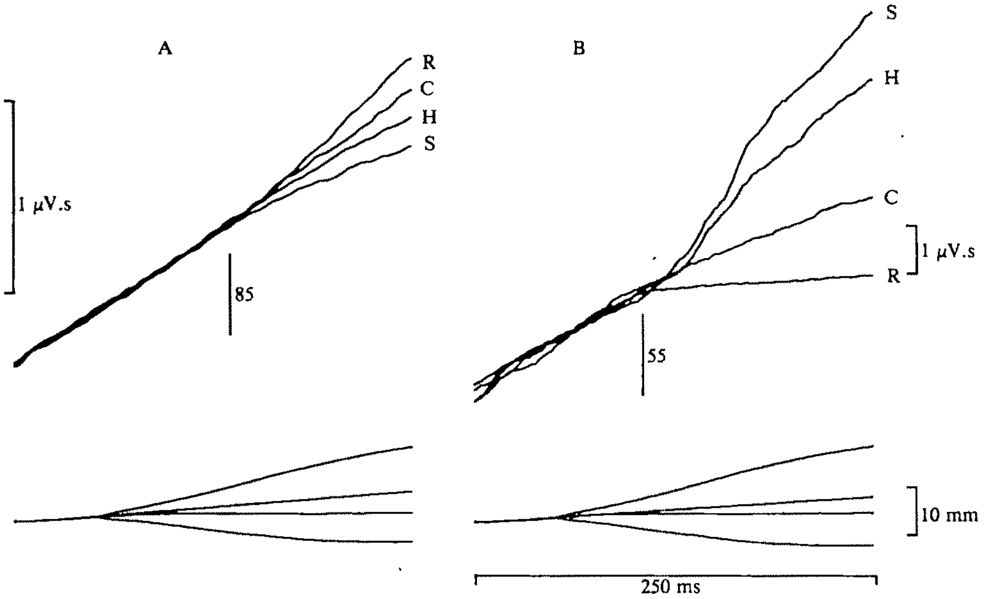

FIG. 7. Stabilization of the crossed hand (the 'teacup' experiment). The kneeling subject pulls on the wire with his left wrist in the ordinary way and meets with the usual perturbations. The lower records give the displacement of the left wrist. The upper records are from the right triceps. In A, the right wrist is slung and the fingers of the right hand touch a dangling 100 g weight (a surrogate teacup). In B, recorded at the same session, the right hand grips the table top (as in fig. 4). The responses in the tulip in A are inverted (as if to stabilize the position of the right hand in space), as compared with the ordinary postural tulip in B. The timing lines are 85 and 55 ms after the time of the perturbations. Each trace in A is the average of 48 trials; in B, of 8 trials. May 8, 1977.

Perturbations to the Trunk

The stabilization of posture when perturbations are encountered by an active hand itself is one contingency, but it must also be necessary to deal with disturbances impinging on other parts of the body. The responses in the teacup experiment can be looked at in this light, if holding the cup is regarded as the prime task and what happens to the other arm as adventitious. As regards the trunk it was of great interest, and something of a surprise, to find modest but early postural responses from applying our standard perturbations (+270 g and −180 g) direct to the pelvis. Such forces, it can be calculated, are roughly equivalent to those exerted on the body by puffs of wind at a strength of 1 or 2 on the Beaufort scale, that is to say, very light puffs. And, by the calculation on p. 518, they cannot produce movements of the whole trunk of more than a few micrometers in the first 20 ms or so.

Fig. 8A–C shows the responses in the thigh muscles to perturbations applied to the hips of a kneeling subject. For fig. 8D–F the subject held the table top with his right hand, as for the crossed-triceps experiments (figs. 4 and 5), and postural responses were recorded from the right triceps. In this experiment perturbations were applied through a yoke bearing on skin over the sacrum, which was anæsthetized to exclude superficial (but not deep) pressure sensations. Movement of the pelvis was recorded photoelectrically and shows, as expected, no detectable movement in the first 25 ms; but after that movement of the trunk gets going much earlier than in the experiments with tensor fasciæ latæ and flexor hallucis longus (fig. 2) with perturbations to the thumb. The response in triceps is at 65 ms, some 40 ms later. The evidence is compatible with the view that body sway is not responsible for the postural tulips earlier described in tensor fasciæ latæ and flexor hallucis longus, but does cause the responses in triceps (also 'driven' as shown by recording shoulder position) in these trunk experiments. A similar experiment (fig. 8G–I) was done recording the position of the head. The head moves late (fig. 8H) and in a direction contrary to the pelvis (the trunk presumably swivelling about its centre of gravity). This experiment makes it very unlikely that information from the otoliths is used in these postural responses. Their mechanism, whatever it is, displays remarkable sensitivity and rapidity of action; but it is worth remembering that similar behaviour was seen with load changes of ±2.5 per cent in the crossed-triceps response (fig. 5A and B). The

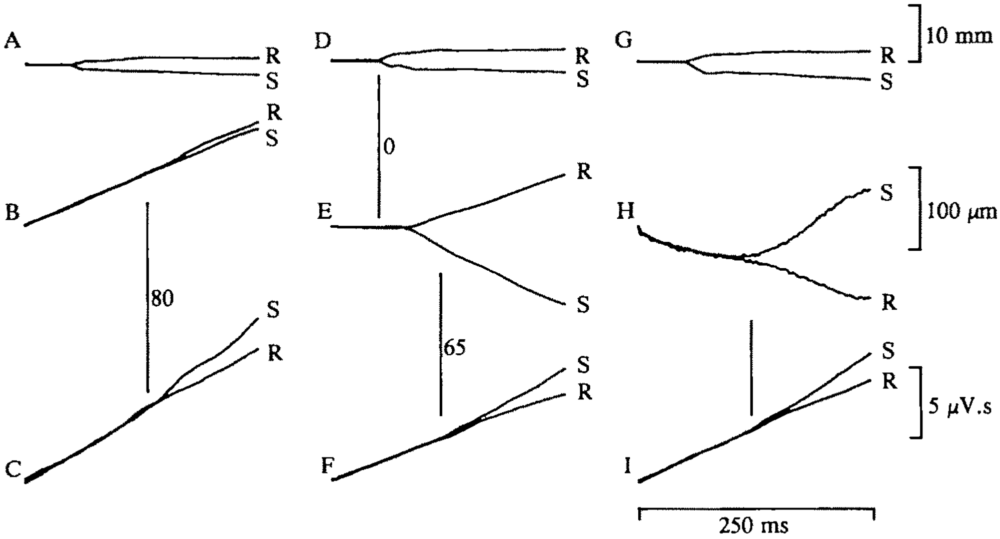

FIG. 8. Postural responses to perturbations applied to the trunk. The motor pulled on the pelvis with the usual initial force of 300 g (2.9 N). The subject kept still and did not track. Pulls and releases only, of the standard size, were applied in random cyclic order and at random intervals of around 3 s. A–C, responses from thigh muscles. The pull was taken by a rope round the hips. A, gives the linear movement of the connecting wire from the motor; owing to compliance the subject moves later and less. B, records from quadriceps femoris with the subject leaning slightly backwards. C, from another similar run; records from hamstrings with the subject leaning forwards. Each trace is the average of 16. January 29, 1977. D–F, an experiment in which the subject steadied himself by holding the table with his right hand. To avoid interference with the displacement recording, the pull of the wire was taken by a yoke passing round the trunk and bearing only on the sacrum (the skin of which had been anæsthetized). F, responses from the right triceps. E, displacement of the pelvis recorded photoelectrically with the pea-bulb stuck on to the right hip. Movement of the pelvis towards the motor causes the trace to move downwards. Each trace is the average of 64. January 30, 1977. G–I, similar to the last experiment but recording head movement (H), with the pea-bulb on a tightly fitted spectacle frame. Movement of the head towards the motor causes the trace to move downwards. Each trace is the average of 64. November 5, 1977.

decelerations (upper limits, respectively 0.4 per cent of *g* and 0.6 per cent of *g*) and the consequent retardations etc., to be detected, come out nearly the same in the two cases. However enigmatic these results are felt to be, they certainly show that few clues and few milliseconds are wasted by the central nervous system in generating postural tulips.

Types of Response in Flexor Pollicis Longus

The standard crossed-triceps experiment (figs. 4 and 5) can be rearranged so that flexor pollicis longus, instead of triceps, is a postural muscle in the right arm. The subject steadies himself by pressing on the frame at head height with the pad of the right thumb. If he pulls on the wire with his left thumb (as for fig. 5) good 'reflex' and 'driven' postural tulips can be obtained in simultaneous recordings over the two flexores pollicis longi. In P.A.M. the postural tulip is 22 ms later than the ordinary 'reflex' tulip in that muscle. (Changing the hands round makes no difference.)

Another experiment, done early in this investigation, suggests that there may be more than one type of 'reflex' tulip in the long thumb flexor. The general arrangements were the same as used in the experiments on postural tulips in pectoralis. The usual movement, with the wire round the tip of the thumb was executed, however, by adducting the arm at the shoulder, with the pendant arm otherwise free. The thumb was held straight out resting against the base of the index finger. The thumb tulip obtained is shown in fig. 9B. In another run, a clamp for the proximal phalanx of the thumb was arranged so that it could be applied to the thumb of the pendant

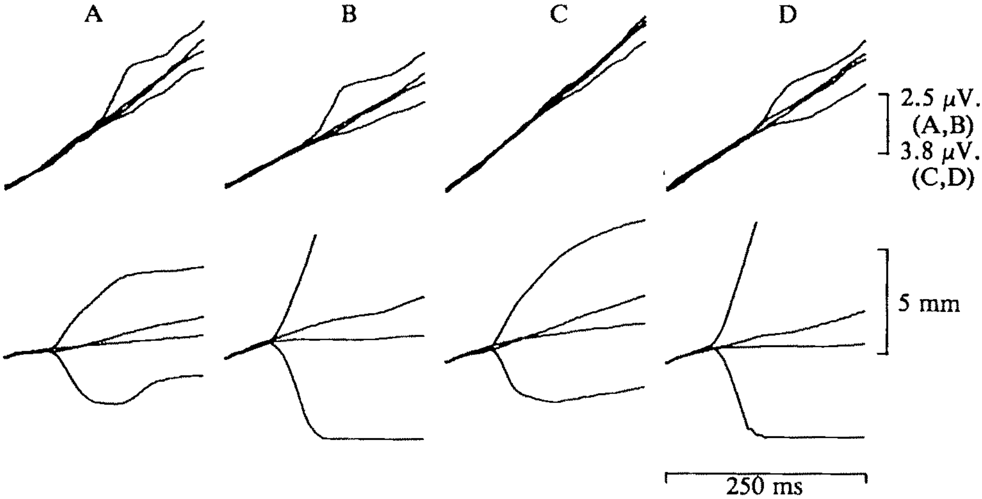

FIG. 9. The differential effect of anæsthesia of the right thumb on contractions of the flexor pollicis longus when it acts either as the sole prime mover or, alternatively, in a quasi-postural role. In each column, thumb tulip above, displacement of wire loop round pad of thumb below. The demanded movements were small enough to be carried out with the proximal phalanx clamped. A, before anæsthesia, proximal phalanx clamped. B, before anæsthesia, arm free. C, thumb anæsthetic (*see text*), proximal phalanx clamped, tulip depressed. D, thumb anæsthetic, arm free, tulip unaffected. Each trace is the average of 8 trials. September 19, 1976.

arm, which hung in the same way as for the run of fig. 9B. With the proximal phalanx thus clamped, the wire was pulled on by flexing the top joint of the thumb, as in the earlier experiments with flexor pollicis longus as a prime mover (Marsden *et al.*, 1976*a*). The amplitude of the movement was the same as when the whole arm moved. These runs gave the tulip in fig. 9A, which is not distinguishable from that in fig. 9B. A cuff was then inflated round the wrist for the usual period of about 80 min, until the hand was anæsthetic. With the arm free and movement from the shoulder the tulip obtained from the thumb flexor (fig. 9D) did not differ from that seen before (fig. 9B). With the proximal phalanx clamped, however, the tulip from flexing the thumb was much depressed (fig. 9C), as it often is with an anæsthetic hand (Marsden *et al.*, 1972, 1977). This experiment has been performed three times on subject P.A.M. and once on subject C.D.M., with concordant results.

This differential effect of anæsthesia is evidence for two modes of activation of flexor pollicis longus. We originally argued, on Jacksonian lines (Marsden *et al.*, 1976*c*), that the first type of movement, from the shoulder with the thumb stationary relative to the hand, would give the long flexor a quasi-postural synergistic function, and that we might demonstrate its distinct mechanism through the differential sensitivity to hand anæsthesia of the responses in the more-automatic postural contraction as compared with those in the more-voluntary prime-moving mode. Whatever the merits of this interpretation, the experiment gave the expected answer.

DISCUSSION

The body is revealed as possessing many quick subconscious mechanisms for adjusting posture, in our experiments shown when the *status quo* was unexpectedly threatened by a perturbing force applied to an extremity or elsewhere. The muscles that contract or relax are only those that are in a position to assist with posture, and if conditions are altered their responses may vanish; we have described instances of this. Of course, distant postural muscles are expected to contract by local reflexes to maintain and restore balance, but what was unexpected was the discovery that they react so very quickly. Indeed, their responses are often so rapid that they start before posture begins to be disturbed and can, in the true sense of the word, be said to anticipate: parts of the body are braced in advance, before the effects of a perturbation reach them—the very reverse of the conventional Sherringtonian chain-reflex. These reactions are not due to reflex arcs from the muscles in which they occur, but are driven by reflex inputs set up *via* the part of the body on which the perturbation impinges. For short, they are referred to as 'driven' responses. The 'driven' nature of many of the responses studied was not easy to establish clearly and, as we have seen, much experimental effort was put into the problem.

One difficulty is that postural responses prove to be extremely sensitive, so that it is difficult to be certain that not enough movement has spread to a distant muscle to elicit a reflex in it. The great sensitivity displayed is of interest on its own account.

As an instance, an extra retarding force of 7.5 g applied to the left wrist was found to elicit a postural contraction in the opposite, right triceps about 60 ms later (fig. 5A). To leave time for conduction along nerves and for events in the central nervous system, the retardation produced by the extra 7.5 g must have reached threshold and been sensed fairly early in the latent period of 60 ms, say in the first 20 ms. Now, as shown on p. 522, 7.5 g applied to the effective mass of the forearm for 20 ms will produce a retardation of the wrist of 12 μm at the most. So the threshold retardation is of the order of the diameter of a red blood cell. Another way of looking at it is to say that an acceleration 0.6 per cent of that due to gravity is sensed in a fiftieth of a second. This acceleration is the same as that of a ball on a smooth plane inclined 0.3 deg to the horizontal. For the postural reactions obtained by pulling directly on the trunk (fig. 8) the displacements or accelerations to be sensed come out much the same. Similar or greater sensitivity is found in the long flexor of the thumb, acting directly as a muscle of prime movement, which can respond to load changes of only 1 per cent (Marsden *et al.*, 1979).

This very sensitivity makes it difficult to pin down the sensory receptors involved, and we do not claim to have done so. Such indications as there are, from peripheral anæsthesia, for example, suggest that they are the muscle receptors, whose *raison d'être* in such unexplainedly large numbers may be to make these rapid and delicate judgements; the averaged input from a multiplicity of receptors would be an advantage in such tasks, as we have argued before (Marsden *et al.*, 1972).

As regards the mode of generation of 'driven' responses, it seems improbable that they are thrown into action by the γ route, in the manner proposed for initiating muscular contraction in the original servo theory. As compared with a mechanism using a reflex arc from the perturbed extremity to the brain and thence from the brain to the distant postural muscle, γ activation would entail two extra conduction delays, one out in the slow γ pathway and one back in the spindle afferents—four journeys in all. But the observed latencies of distant postural tulips allow us only about half the time required for four conduction delays; for example, using both long thumb flexors (p. 528), the 'driven' tulip is only 22 ms later than the ordinary 'reflex' tulip at 45 ms, so only about 20 ms would be available for the extra journeys, whereas something well over 45 ms (bearing in mind the slow conduction in γ fibres) would seem to be required. In flexor hallucis longus the shortfall is even more pronounced, for the latency (100 ms) of the postural tulip (fig. 2G) is little longer than that of the direct stretch reflex (90 ms, Marsden *et al.*, 1976*b*). Possibly these difficulties might be circumvented, but it is not obvious how.

The relation between 'driven' responses and the stretch reflexes in the postural muscles is obscure. Reflex responses to stretch, mixed in randomly with driven responses, have been seen in experiments (not here reported) using two motors, both in pectoralis and in the ankle extensors; so the muscles are apparently available at the same time for both reflex and driven responses. When they occur simultaneously, it was found that the driven responses largely override the stretch reflex in some as yet obscure way.

On a more speculative plane, the similarity in general appearance and in latency of 'reflex' and 'driven' tulips, which has been striking throughout the investigation, raises the possibility that they may both be generated by similar central mechanisms and perhaps in the same, so far unknown, part of the brain—to adopt the plausible conjecture that we are dealing with the cerebrum or cerebellum rather than with the spinal cord. Thus the central mechanisms might use afferent signals from the prime mover to generate the 'reflex' tulip in that muscle, and use the same signals in a similar way to generate 'driven' postural tulips in distant muscles. The latter process is clearly not quite the same; it is slower, presumably because there is more to be taken into account, and the latency of the responses is more obviously variable than of those in prime movers: the latency of the tulip in tensor fasciæ latæ in some early experiments was significantly longer than in that of fig. 2 a year later; late responses are also seen in figs. 3B and 4C. Again, there is not much to choose between the latencies of the tulips in erector spinæ and hamstrings (fig. 3), whereas one might expect that the spinal muscles, with their shorter conduction distances, would come in substantially earlier. The latencies of ordinary reflex tulips seem to be more regularly arranged. But, by and large, the similarities of 'reflex' and 'driven' tulips (and of their behaviour) remain impressive.

Lastly we recall the three curious ways in which the unconscious motor system has let us see some of its previously hidden performances.

First, there is the need, not always present to start with, but later imperative, for large perturbations to be presented if the system is to function at full sensitivity. Exactly the same need is found both with postural and prime tulips (Marsden *et al.*, 1979). This phenomenon may have to do with a system for ignoring small perturbations as trivial, unless there are (unconsciously perceived) reasons for thinking they are not. There it must be left to await more evidence.

Then, there is the way in which postural responses in the right arm are upset by temporarily substituting a handle that goes floppy, for the usual fixed grip. Responses may remain depressed for a long period after the fixed grip is restored; and there are other odd happenings. They are something to do with a purely subconscious system that uses sensory clues to judge the suitability of external objects for postural support and then decides (sometimes in an unexpectedly petulant way that the subject cannot voluntarily get the better of) whether to use them or not. As we have already argued, muscles appear only to take part in postural responses if conditions are such that they can do something to help.

Thirdly, there is the system, presumably allied to the last, which decides (again wholly subconsciously) that an external object is to be handled like a cup of tea, rather than as a postural support, and engages the appropriate mechanism for generating reversed responses. This has merely been demonstrated to occur and, like many of the new phenomena described, awaits investigation; but perhaps more than any other experiment it shows the ability of the system we are dealing with to evaluate complex situations and to adapt the rapid automatic responses of the subject in an apparently purposive way.

These three phenomena, appearing incidentally, paint for the first time a picture of an unconscious motor system generating these responses but behaving almost wilfully (independently, however, of the subject's conscious will), with unsuspected rules of its own against which the physiologist fences in order to understand them. One wonders whether games players and other skilled performers may not unconsciously fence against them too, when they are trying to reach their form. We have been dimly aware of something of the kind since 1971 as that which made our halt responses labile (Marsden *et al.*, 1976*a*) and interfered in other ways. Now the picture has begun to emerge, other phenomena can be seen as candidates to be fitted into it: the mysterious effect of anæsthesia of the thumb on tulips in the long flexor and the effect of a visual display in reversing that effect; various phenomena connected with anæsthesia in this paper; the properties of postural responses to head-bending to be discussed elsewhere. And there must be many more undiscovered.

SUMMARY

1. During a voluntary movement with the arm free and the load taken by the thumb, records of servo-like responses to unexpected perturbations (known as 'tulips') were made, as previously described, from the long flexor of the thumb. Similar tulip-like responses, identified as postural, at much the same latency of about 40 ms, were found in pectoralis major and, if the subject's stance was suitable, at a longer latency in tensor fasciæ latæ, in the long flexor of the big toe and (Traub *et al.*, 1980) in the ankle extensors. The perturbations used were always relatively small, the largest being 270 g (2.6 N).

2. With the subject kneeling, the load taken on the wrist and the prime movement flexion of the elbow, tulip-like early postural responses were picked up from erector spinæ, from the extensors of the knee and from hamstrings. If the subject used the opposite hand to steady himself, brisk postural responses appeared in biceps and triceps of that arm, or even, with special arrangements, in flexor pollicis longus (so postural responses are not confined to special postural muscles).

3. A sensitive photoelectric method was used to monitor sway of relevant parts of the trunk while such postural tulips were recorded. In the latent period of the responses, trunk movement related to the perturbations was virtually absent and was certainly less than a few micrometres. So it appeared that these early postural reactions were not caused by disturbances of posture but anticipated them.

4. The evidence is that anticipatory postural tulips are not due to reflexes arising in the postural muscle itself but are 'driven' by afferent inputs from the parts of the body on which perturbations impinge. The distinction is thus drawn between autogenetic 'reflex' tulips in prime-moving muscles and heterogenetically 'driven' postural tulips in distant postural muscles—'driven' from receptors not in those muscles.

5. Another possible indication that postural tulips use a different nervous mechanism from those previously investigated in prime movers was that anæsthesia

of the thumb did not depress the tulip in flexor pollicis longus when it was used in a quasi-postural role, but, as already described in earlier papers, did depress the tulip in movements in which flexor pollicis longus was the prime mover.

6. The 'driven' postural mechanisms are very sensitive and can respond to changes of load on the thumb of only 7.5 g (0.074 N), which are less than would appear to offer a threat to the stability of the body, and which are below even the forced-choice threshold for perception by the subject.

7. Perturbations of the usual size applied to the trunk itself also caused early postural responses. Because of the mass of the trunk the mechanism of such responses must be very sensitive; but it turns out to be no more so, relatively, than for small perturbations applied to a limb.

8. If the right hand gripped an object to steady the body against perturbations applied to the left hand, postural responses were not, in general, seen in the right arm unless the object gripped was a firm and reliable support. Thus they failed (and were difficult to recover later) if the support intermittently went limp.

9. If, with the usual task for the left hand, the right hand touched or held a body of low inertia, the tulip responses in the right arm became inverted as if to keep the right hand in the same place in space. These inverted postural responses are interpreted as those needed to steady a cup of tea, held in the right hand, against perturbations encountered elsewhere. Inverted responses emphasize the point that the postural responses described in the paper, although automatic, are as well adapted to the task currently in hand as if they were voluntary; and they must have a complex nervous mechanism, presumably cerebral or cerebellar.

ACKNOWLEDGEMENTS

C.D.M. and P.A.M. express their thanks to Dr W. A. Cobb in whose Department of Clinical Neurophysiology at the National Hospital the experiments were done. Financial support was received by C.D.M. from the Bethlem Royal and Maudsley Hospitals Research Fund and by P.A.M. from the Department of Industry.

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—— —— —— (1976*c*) Servo action in human posture. *Journal of Physiology, London*, **263**, 187–188*P*.

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(*Received September 30, 1980*)

Brain (1981), **104**, 535-558

THE FAMILIAL OCCURRENCE OF CREUTZFELDT-JAKOB DISEASE AND ALZHEIMER'S DISEASE

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INTRODUCTION

IN our epidemiological study of 1435 cases of Creutzfeldt-Jakob disease (CJD), more than 15 per cent occurred within families with two or more affected members (Masters, Harris, Gajdusek, Gibbs, Bernoulli and Asher, 1979*b*). Preliminary analyses of the familial occurrence of CJD have been presented (Ferber, Wiesenfeld, Roos, Bobowick, Gibbs and Gajdusek, 1974; Masters, Gajdusek, Gibbs, Bernoulli and Asher, 1979*a*). In this paper we present a more detailed analysis of 27 of the 73 families with CJD that we are studying, and examine the possible modes of transmission. The disease occurs in a pattern consistent with autosomal dominant transmission, and is therefore the unique example in man of a virus-induced disease apparently determined by a single gene mechanism. However, the available data do not allow us yet to distinguish between an inherited susceptibility to infection, some form of vertical transmission, or a common environmental source of infection. The results of this study do suggest that the familial CJD infection is acquired post-natally, and are consistent with the suspected mechanism of transmission of natural scrapie, where in a genetically susceptible host, infection is acquired largely in the first six months of life, possibly through the alimentary tract.

Alzheimer's disease (AD) shares a number of clinical and pathological features in common with CJD, and also occurs in familial aggregates. In this paper, we compare and contrast the familial occurrence of AD with CJD, and discuss the possibility that AD might also have an infectious cause.

MATERIALS AND METHODS

The data on the families with CJD were collated either from cases referred to our laboratory (55 families) or from cases published in the literature (26 families). For 8 families reported in the literature by others we have from our records additional unpublished data. Families with AD were similarly collated from those referred to our laboratory and those published in the literature. The CJD and

AD families are divided into four groups, namely: A, familial CJD; B, familial AD, with at least one member with definite AD; C, familial AD, with at least one member affected with definite CJD; D, familial AD, where one or more members have a clinical syndrome resembling CJD, but have pathological changes only of AD.

In the first section of the Results, we analyse in detail the familial occurrence of CJD and AD based on Groups A and B above. The aspects examined include ages at onset and death, sex distribution, duration of illness, rates of occurrence of disease among siblings and cousins, peculiarities of the genealogies, conjugal occurrence, twin occurrences, evidence for preponderance in maternal or paternal line relations, and evidence for anticipation. Temporal and spatial separation between affected family members, death intervals, and differences between ages at death of affected siblings are also presented. The clinical and pathological findings, and occupational and past medical and surgical histories of CJD-affected members are compared to those patients with the sporadic form of CJD (Masters *et al.*, 1979*b*). Comparisons of age at death, duration of illness, and sex ratios between sporadic and familial CJD are based on the data obtained from 112 cases of sporadic CJD from which virus causing an experimental spongiform encephalopathy was isolated from the brain (Masters *et al.*, 1979*b*). Comparable data for the comparison of the sporadic with the familial form of AD are not available.

In the second section of the Results, we present data on Group C and D above which pertain to the possible common pathogenesis of CJD and AD. In the final section of the Results, we present the experimental data on the transmissibility of familial CJD and report on the attempts to isolate an infectious agent in familial AD. The most recent data on the distribution of the virus of CJD in body tissues and effective routes of inoculation are summarized and discussed in relation to the possible modes of transmission of the virus in familial CJD.

The composition of families in Groups A, B, C, and D is summarized below:

Group A. Familial CJD

A total of 73 families with two or more members affected with CJD (with definite, probable or possible CJD, diagnostic categories as defined previously (Masters *et al.*, 1979*b*)) were identified from a total of 1902 cases of CJD worldwide (as of March, 1980). Within these 73 families, there were 286 affected members, yielding a proportion of 15 per cent familial occurrence of CJD. From these families, we selected 27 families in which 2 or more members were affected with definite CJD (histologically verified spongiform encephalopathy) or probable CJD (diagnosed on clinical criteria alone), with a total of 130 affected members, and use this group of 27 families as the basis for the analysis of the familial occurrence of CJD in this paper. This total of 130 affected members comprised of 47 cases of definite CJD, 47 cases of probable CJD, and 36 cases of possible CJD. In the remaining 46 families, either only one member had a definite or probable diagnosis of CJD (with other members diagnosed as possible CJD), or atypical forms of CJD occurred, some of which are described elsewhere (Masters, Gajdusek and Gibbs, 1981). Also excluded from the present analysis are families with the amyotrophic form of CJD, a non-transmissible form of amyotrophic lateral sclerosis with dementia (Salazar, Masters, Gajdusek and Gibbs, 1981).

Brain tissue, and in some cases tissues from other organs, from 28 affected members in the group of families with CJD were studied experimentally for the presence of virus. These specimens were prepared and inoculated into nonhuman primates and other laboratory animals by methods described previously (Gibbs, Gajdusek, Asher, Alpers, Beck, Daniel and Matthews, 1968).

Group B. Familial AD, with at least One Member with Definite AD

This group is comprised of 52 families with 2 or more members affected with definite AD (histologically confirmed) or probable AD (diagnosed on clinical criteria alone). Within this group, there were 229 affected members, comprised of 82 cases of definite AD, 83 cases of probable AD, and 64 cases of possible AD. Details of these families, with sources and references, are listed elsewhere (Masters *et al.*, 1979*a*).

Brain tissue from 14 affected members in these families have been inoculated into nonhuman primates in an attempt to demonstrate the transmissibility of AD.

Group C. Familial AD, with at least One Member Affected with CJD

There were 4 families where pathologically confirmed spongiform encephalopathy characteristic of CJD occurred in one member while 2 or more members had AD. In 2 of these 4 families, 2 or more AD affected members were definite or probable AD, and in the other 2 families, 2 or more AD affected members were possible AD. Brain tissue from 2 cases diagnosed as CJD and one case diagnosed as AD were available for animal inoculation studies.

Group D. Familial AD, where One or More Members have a Clinical Syndrome Resembling CJD

There were 17 families where 2 or more members had AD, at least one pathologically verified, and in whom the rapid progression of dementia accompanied with abnormal movements (particularly myoclonus), together with pyramidal, extrapyramidal or cerebellar signs, or periodic sharp wave complexes in the EEG, might otherwise have led to the clinical diagnosis of CJD. Twelve of these families are published in literature (referenced in Masters *et al.*, 1979*a*). Brain tissue from affected members in 7 families were available for animal inoculation studies.

RESULTS

I. *Descriptive, Genealogical, and Temporal-spatial Analyses of Familial CJD Compared to Familial AD*

Table 1 summarizes the countries of origin, number of affected members and number of affected generations in each of the 27 families with CJD selected for analysis. Representative abbreviated genealogies of 12 of these families are illustrated in figs. 1 and 2. In the 27 families with CJD, there were a total of 130 affected members (average 4.8 affected members per family), and in the 52 families of AD, there were a total of 229 affected members (average 4.4 affected members per family). The ancestries of most of the North American CJD families can be traced to Europe, particularly to Eastern Europe (Hungary, Czechoslovakia and Poland, *see* Table 1), consistent with the ancestries of many Americans.

In general, the clinical and pathological findings in cases of familial CJD and AD did not differ substantially from those of the sporadic form of the disease. The same was true for AD. Three CJD-affected members in 2 families (Families T.A. and M.D.) were originally diagnosed as Huntingdon's disease, but in retrospect had typical CJD. Four CJD affected members in 3 families (Families C.K., M.M. and R.G.) had prominent vertical gaze palsies, suggesting a diagnosis of progressive supranuclear palsy, but the progression of the disease eventually evolved into typical CJD. The propositus in one family (Family L.S.) had been admitted to hospital for chronic paranoid schizophrenia for ten years before the onset of otherwise typical CJD. All pathologically verified cases of CJD had the typical changes of a spongiform encephalopathy, with the exception of 2 cases in the Family G.M. in which the spongiform change, although present, was irregularly distributed within the cerebral cortex, striatum and thalamus. Overall, differences in clinical and pathological findings within families were less than between families.

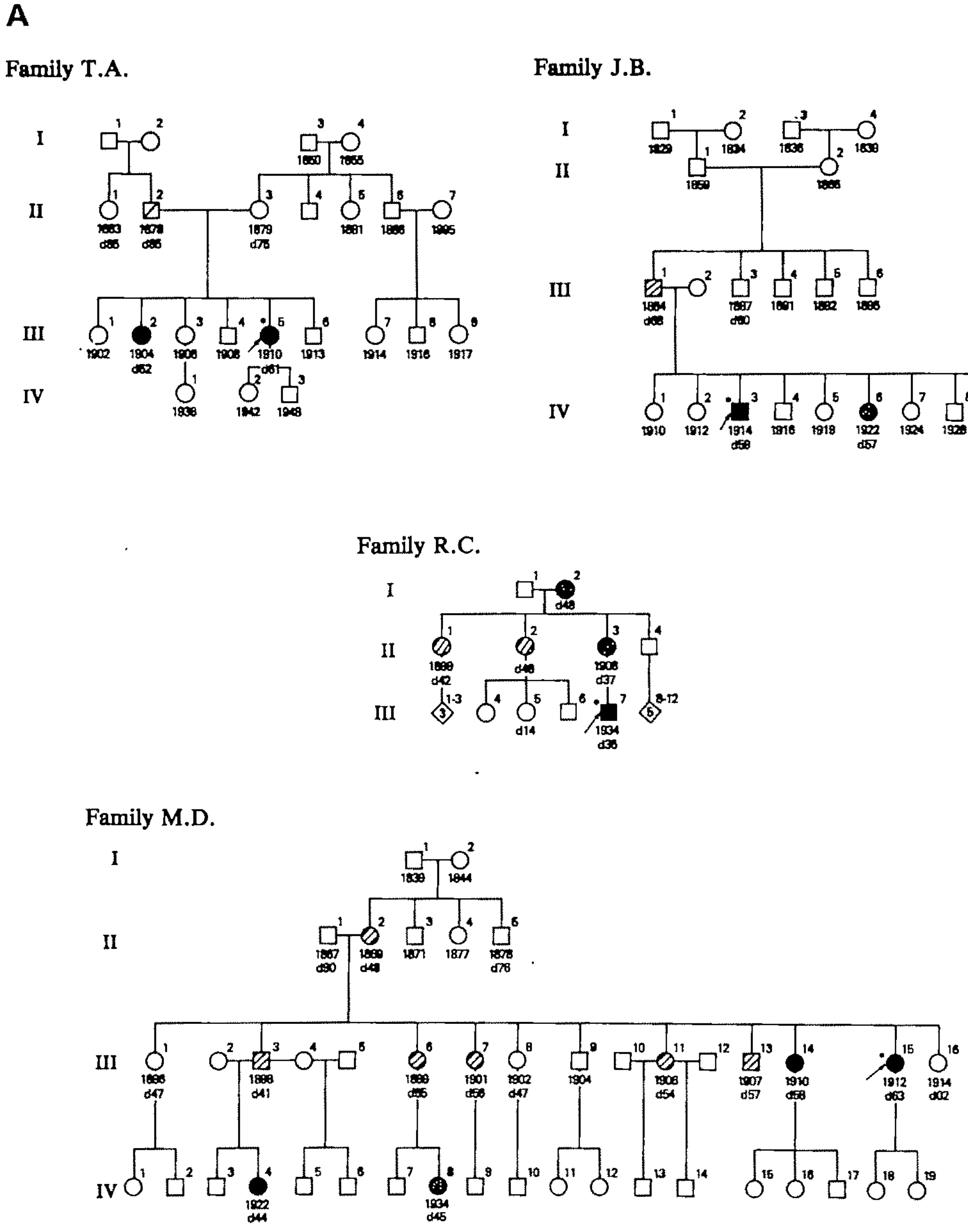
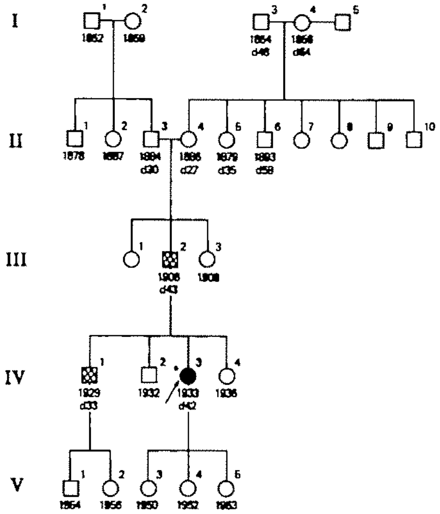


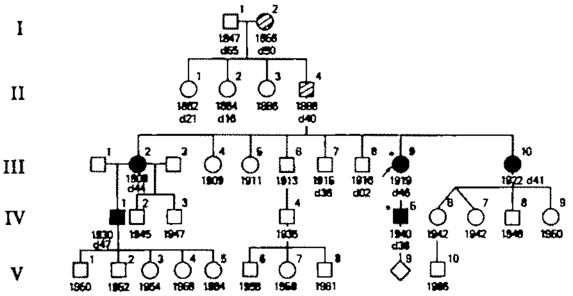
FIG. 1A and B. Representative genealogies of seven families affected with CJD, in which brain tissue from at least one affected member has been inoculated into nonhuman primates (indicated by an arrow) and caused an experimental spongiform encephalopathy (indicated by *). Where known, the year of birth and age at death (indicated by d) are shown. Black circles or squares indicate definite CJD, cross-hatching represents probable CJD, and diagonal hatching indicates possible CJD. *See* Table 1 for references and sources for each family.

B

Family L.S.



Family S.T.



Family M.W.

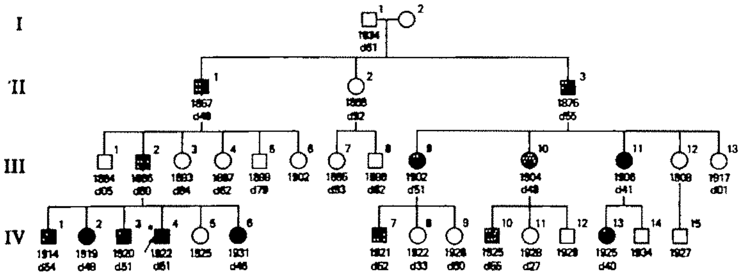


TABLE 1. FAMILIES WITH CJD. COUNTRIES OF ORIGIN AND NUMBER OF AFFECTED MEMBERS AND GENERATIONS[1]

	Family identification[2]	*Country of origin*	*No. of affected members/ No. of affected generations*
1.	T.A.*	Hungary/Slovakia, migrated to USA in 1900	2/1
2.	J.B.*	Bohemia/Slovakia, migrated to USA in 1883	3/2
3.	R.C.*	France	5/3
4.	M.D.*	The Netherlands, migrated to USA in 1894	10/3
5.	C.K.*	Hungary, migrated to Canada 1957	6/1
6.	M.W.*	West Germany	2/1
7.	L.S.*	Probable German origin, migrated to USA in 1850s	3/2
8.	S.T.*	Hungary/Romania, migrated to USA in 1911	7/4
9.	M.W.*	France	14/3
10.	A.An.C.*	Chile	3/2
11.	Backer	Germany, with migration of one affected member to USA in 1940s(?)	15/4
12.	A.B.†	France	3/2
13.	Bori	Hungary	2/1
14.	E.Co.M.†	Chile	8/2
15.	A.F.†	France	4/1
16.	R.G.†	France	3/2
17.	A.Go.A.†	Chile	2/1
18.	H	Japan	2/1
19–22.	Four Israeli families	Libya with migrations to Israel	4/3, 2/1, 2/2, 2/2
23.	G.M.†	USA, since early 1800s	6 (possibly 7)/3
24.	I.P.†	Poland, migration to USA in early 1900s	3/2
25.	D.S.†	French Canadian, since mid 1800s	5/3
26.	O.S.†	Finland, with migration of one member to The Netherlands	10/3
27.	H.W.†	Canada, since mid 1800s	2/1

[1] The abbreviated genealogies of Families T.A., J.B., R.C., M.D., L.S., S.T., M.W. and A.B., G.M., D.S., O.S., H.W. are illustrated in figs. 1 and 2. [2] In the families denoted by *, virus causing an experimental spongiform encephalopathy has been isolated from the brain of an affected member. In the families denoted by †, virus isolation studies are still in progress.

References and sources of referral of each family as follows: 1. Drs K. Johnson and B. Banker, Ohio; 2. Dr J. Davenport, Washington and Dr B. White, Ohio; 3. Bonduelle, Escourolle, Bouygues, Lormeau, Ribadeau-Dumas and Merland, 1971; 4. Dr W. Isgreen, New York and Dr H. L. Chodosh, New Jersey; 5. Dr J. Deck, Toronto; 6. Dr W. Krücke, Frankfurt and Drs G. Paal and A. Struppler, Munich; 7. Dr M. Jones, Michigan; 8. Friede and De Jong, 1964; May, Itabashi and De Jong, 1968; 9. Buge, Escourolle, Brion, Rancurel, Hauw, Mehaut, Gray and Gajdusek, 1978; Cathala, Chatelain, Brown, Dumas and Gajdusek, 1980; 10. Galvez and Cartier, 1981; 11. Kirschbaum, 1924, 1968, 1971; Meggendorfer, 1930; Jacob, Pyrkosch and Strube, 1950; 12. Guidon, 1978; 13. Majtényi, 1975; 14. Galvez *et al.*, 1980; 15. Dr F. Cathala, Paris; 16. Drs K. Braun and S. Lakshmanan, New York, and Dr F. Cathala, Paris; 17. Dr S. Galvez, Santiago; 18. Akai, Kato and Oyanagi, 1980; 19-22. Neugut, Neugut, Kahana, Stein and Alter, 1979; 23. Drs H. Tamm and E. David, Maine; 24. Drs R. Sherbert and R. Daroff, Florida and Dr S. C. Leonberg, New Jersey; 25. Dr B. Katz, Massachusetts and Drs S. Pogacar and M. Ambler, Rhode Island; 26. Haltia *et al.*, 1979; Kovanen *et al.*, 1980; 27. Dr K. Livingstone, Toronto.

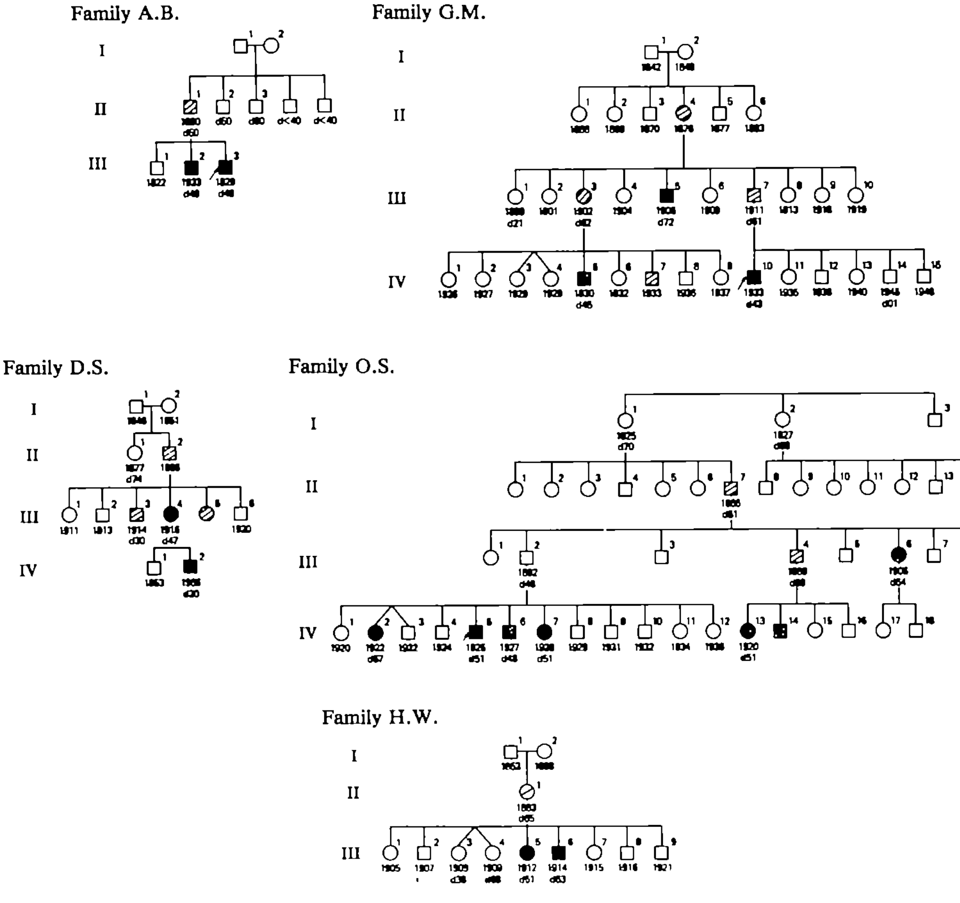


FIG. 2. Representative genealogies of five families affected with CJD in which studies on the transmissibility of brain tissue from at least one affected member are still in progress. Notations in the genealogies are explained in the legend to fig. 1.

TABLE 2. MEAN AGES AT DEATH, DURATION OF DISEASE AND SEX RATIOS IN FAMILIAL AND SPORADIC CJD AND FAMILIAL AD

Mean ages at death

	No. of cases	*Mean age at death (yrs)*	*SD*	*Range*
Familial CJD	110	51.1	9.6	20–73
Sporadic CJD	112	57.8	9.7	19–78
Familial AD	98	55.9	10.6	26–85

Mean duration of disease

	No. of cases	*Mean duration of disease (months)*	*SD*	*Range*
Familial CJD	79	10.5	9.3	1–51.5
Sporadic CJD	105	8.1	7.9	1.5–55.0
Familial AD	78	84.7	59.2	12–300

Sex ratios

	No. of males	*No. of females*	*Ratio (M:F)*
Familial CJD	58	64	0.91
Sporadic CJD	59	53	1.11
Familial AD	82	134	0.61

Age at death, duration of disease, and sex ratios (Table 2). The mean age at death of cases of familial CJD was 51 years, which is significantly less than the mean age at death of cases of sporadic CJD (58 years, $P < 0.001$) and familial AD (56 years $P = 0.001$). The mean duration of disease in familial CJD (eleven months) is not significantly different from the mean duration in sporadic CJD (eight months), but as expected, is significantly shorter than mean duration of illness in familial AD (eighty-five months, $P < 0.001$). Males and females are nearly equally affected in familial CJD (M:F ratio 0.91), while females are more common in familial AD (M:F ratio 0.61).

The cumulative frequency distribution for age at death in familial and sporadic CJD is shown in fig. 3. As in Huntington's disease (Pericak-Vance, Conneally, Merritt, Roos, Vance, Yu, Norton and Antel, 1979), this curve may be used to determine the probability of disease for at-risk individuals, assuming a dominantly inherited 'gene' for CJD. For example, the most frequent occasion for concern is that of a family member with an affected sibling and an affected parent. If the unaffected member had reached the age of 60 years without developing disease, the probability that he would have developed the disease if he had inherited the 'gene' from his parent is 0.84 (since the data presented are for age at death, an allowance of approximately one year should be made in calculating the age at onset). The probability of being normal at this age if he had inherited the 'gene' is 0.16 (1–0.84).

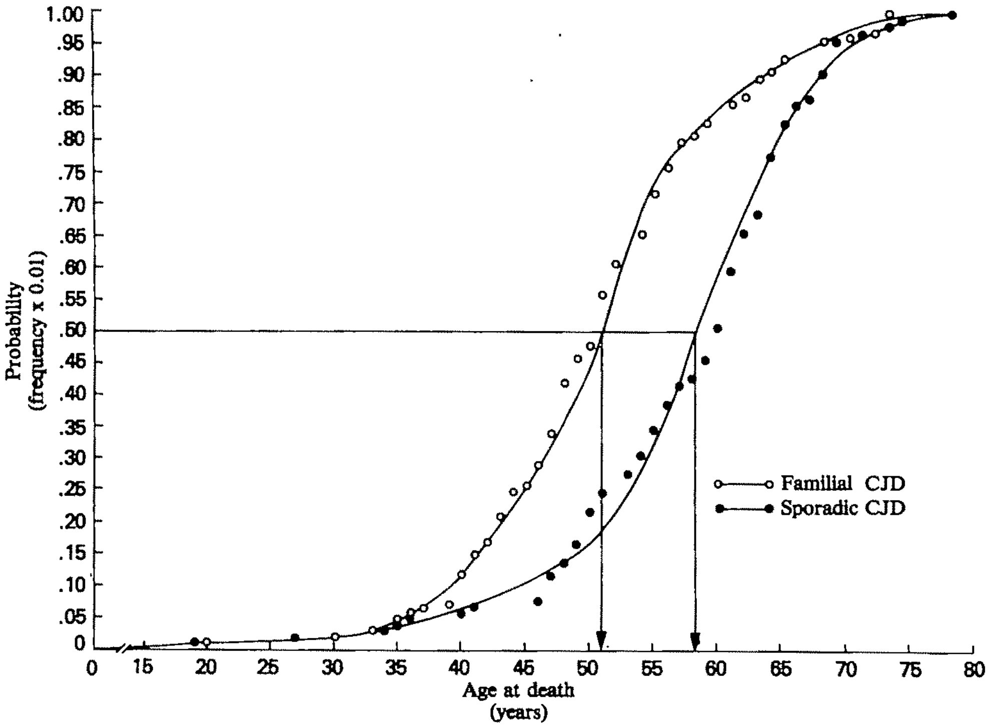


FIG. 3. The cumulative frequency distribution of the ages at death in familial and sporadic CJD. The frequency ×0.01 gives the probability values (*see text*). The mean ages at death (indicated by lines and arrows) show the earlier age at death in familial compared with sporadic CJD.

As there is at present no way of determining prior to onset of disease whether any individual has this 'gene' for CJD, these probabilities have little practical use, but may be of use in future genetic linkage studies.

Proportional incidence of affected members within generations. Most cases of familial CJD and AD occurred within the same generation as, or only one generation above, that of the propositus. This is probably a reflection on the method of case ascertainment, which was based primarily on the anamnestic data provided by members of the family in the same generation as the propositus.

From the number of affected and non-affected siblings aged 40 years or more within any generation with an affected member, it is possible to calculate a proportional incidence or 'rate of occurrence' (Table 3). The proportional incidence among siblings of an affected member in both familial CJD (36 per cent) and familial AD (48 per cent) is consistent with a pattern of autosomal dominant inheritance, where in theory this proportion would be 50 per cent. If only the sibships of affected CJD propositi are considered, the proportion increases slightly to 38 per cent.

Less complete data are available for the proportional incidence of disease for first cousins of propositi, where, with the small numbers available, these proportions were 21 and 20 per cent for familial CJD and AD, respectively (Table 3). It would be expected that, with better case ascertainment, and perhaps setting an age limit above the mean, values of 25 per cent, those expected for a dominant pattern, would be obtained.

TABLE 3. INCIDENCE OF FAMILIAL CJD AND AD IN SIBLINGS AND FIRST COUSINS

	No. affected	*Total No. of siblings or first cousins aged 40 yrs or more*	*Percentage affected*
Proportional incidence in all affected sibships		*Siblings*	
Familial CJD	116	322	36
Familial AD	154	319	48
Proportional incidence in first cousins of propositi		*First cousins*	
Familial CJD	11	52	21
Familial AD	14	70	20

Maternal and paternal lines of inheritance. In the families with CJD, there were 19 affected mothers and 17 affected fathers of affected children. The corresponding numbers in familial AD were 28 and 34. There is therefore no evidence that mothers were more frequently affected than fathers, which could have been taken as a point in favour of vertical transmission. Similarly, there was no evidence that the age at onset or death was different between children born to affected mothers or affected fathers.

Anticipation. Anticipation, a decrease in the age at onset or death of affected members in succeeding generations, was evaluated from the number of instances where the parental age at death exceeded, equalled, or was less than the age at death of an affected child. In familial CJD, there were 33 instances where the parental age at onset or death exceeded or equalled the affected offspring's age at onset or death, while there were 21 instances where the parental age was less than the offspring's age. The corresponding figures in familial AD were 38 and 15, respectively. Thus a tendency for anticipation was observed, the significance of which is difficult to evaluate.

Temporal and spatial separations between CJD affected members. The familial clustering of an infectious disease such as CJD permits a search for evidence of lateral transmission through close physical contact, for evidence of exposure to some common environmental source of infection, or for vertical transmission. Analysis of temporal-spatial separations between cases within a family may also indicate minimum incubation periods assuming that contact transmission occurs.

There were several clear-cut temporal-spatial separations between CJD-affected family members. In the Family M.D. (fig. 1), where 7 of 9 siblings in the third generation were affected (many originally diagnosed as Huntington's disease), the only surviving unaffected member (III-09) had left home at the age of 21 years, and subsequently had little contact with his siblings. In contrast, all affected siblings in this generation lived their adult lives in the same area, and were described as 'close' in terms of their physical relationships or contact. In the Family C.K. (Table 1), the propositus left Hungary in 1957, and subsequently had no contact with any of her five sisters who developed CJD; she developed CJD fifteen years after leaving Hungary. In the Family S.T. (fig. 1), the family migrated to America five years after the death of the affected member in generation I. Sixteen years later, the member in generation II developed possible CJD. In the Family A.B. (Guidon, 1978, and fig. 2), the two affected siblings were separated shortly after the birth of the younger (III-03). They were raised separately, and had no contact with each other at any time during their lives. Both developed CJD at about the same age more than forty years after separation. Finally, in the Family O.S. (Haltia, Kovanen, van Crevel, Bots and Stefanko, 1979, and fig. 2), one affected member (IV-02) lived in The Netherlands for thirty years before her death, but was known to have travelled frequently to Finland where the other affected members lived.

The existence of single families in two continents or countries, each part of the family continuing to have CJD over two or more generations, clearly indicates no common temporal event for infection in all members, and limits the common environmental sources of infection requiring consideration.

Minimum incubation periods for individual cases can often be determined from the historical analysis of temporal and spatial separations within families. In this instance, from the data outlined above, incubation periods of between one and four decades are indicated if contact transmission were occurring. Another approach is to examine the intervals between the death of an affected parent and the onset of disease in the first affected child, which clearly represents a lower limit to the incubation period for the subject under consideration if infection were being passed from generation to generation by contact with ill patients. Within the families with CJD, there were 30 pairs of affected parent/affected first child where the death intervals were known. The mean interval was twenty years with a range of four to forty years.

If affected siblings died at approximately the same time, this could be evidence for common exposure, assuming a constant incubation period. If affected siblings tended to die at the same age, this would be more consistent with vertical transmission, or with infection acquired at birth or early infancy. In this present series, there were 66 sibling pairs where the dates of birth and death were known. The mean difference in the age (that is, the birth interval) of these sibling pairs was 6.6 years, the mean difference in age at the time of death was 0.6 years, and correspondingly, the mean difference of the interval between the dates of death of the sibling pairs was 7.2 years. There was a weak correlation between the birth interval and the difference in age at death ($r = -0.224, P = 0.035$), and a significant correlation between the birth interval and the interval between the dates of death ($r = 0.346, P = 0.002$). These data suggest that affected siblings tend to die at the same age, and not at the same time, and therefore are more consistent with some form of vertical transmission rather than a common point exposure to infection.

Atypical features in the genealogies of familial CJD and AD. Within the 27 families with CJD, there were 9 families in which the disease occurred in a single generation (Table 1). In 6 of these single-generation families, there was insufficient information on the cause of death of the parents, so the possibility of CJD in preceding generations could not be excluded. If the remaining 3 families (T.A., M.M. and H.W.), in each a parent had died from a neurological disease which was poorly characterized (in the Family T.A., the father died from 'severe parkinsonism', aged 85 years; in the Family M.M. the father died from a 'stroke' aged 90 years; and in the Family H.W., the mother died from 'cerebral thrombosis' aged 65 years). Thus, when two or more siblings develop the CJD, the restriction of cases to that single generation is unusual, and calls for a careful search of the family history. Twelve of the 52 families with AD had the disease in a single generation, and in most of these the cause of death of the parents remains unknown.

Skipped generations were observed infrequently, occurring nine times in the CJD families. In one instance, the family member died aged 48 years from an intestinal volvulus (III-02 of Family O.S.); in three instances there was insufficient information on the cause of death (III-02 in Family Backer; II-03 in family E.Co.M.; and II-03 in family R.G.); and in 3 families the disease occurred only in cousins (family H and 2 Israeli families). At present, we have not demonstrated conclusively that familial CJD can skip a generation. Skipped generations occurred only five times in the 52 families with AD, and in each instance, there was insufficient information on the cause of death of the unaffected individual.

Concordant twin occurrences of CJD were not documented. In one family (O.S.—Haltia *et al.*, 1979; fig. 2), a pair of discordant non-identical twins was found. The unaffected twin is at present 58 years and under close observation. Three concordant twins occurred in the 52 families with AD, although isolated discordant monozygotic twins are reported in the literature (Davidson and Robertson, 1955; Hunter, Dayan and Wilson, 1972; Cook, Schneck and Clark, 1981).

Two conjugal pairs of CJD have been described (Jellinger, Seitelberger, Heiss and Holczabek, 1972; Matthews, 1975), but none other has been documented in more than 2,000 cases of CJD now reported to our laboratory. However, 2 cases of possible CJD occurred in members related by marriage in 2 families of CJD (Family E.Co.M.—Galvez, Masters and Gajdusek, 1980; Family A.F., Table I). These conjugal and marriage related cases could be taken as strong evidence in favour of lateral transmission or common source infection. Surprisingly, conjugal cases of AD or cases of AD related by marriage into families with AD have not been reported. We recently observed a wife with CJD and her husband with AD, both dying at almost the same time. The brain of the wife showed many amyloid plaques in addition to the typical spongiform change of CJD.

Past medical, surgical, and occupational histories. In our previous report on the epidemiology of CJD, we commented on the apparent increase in reported surgical procedures and medical illnesses in the histories of patients with CJD (Masters *et al.*, 1979*b*), an aspect of importance when considering the known iatrogenic transmission of the virus (Duffy, Wolf, Collins, Devoe, Streeten and Cowen, 1974; Bernoulli, Seigfried, Baumgartner, Regli, Rabinowicz, Gajdusek and Gibbs, 1977).

In the present series of cases and familial CJD and AD, the number of cases in which complete past medical and surgical histories were obtained was too few to permit any meaningful tabulation. In the histories that were available, there was no clear evidence for iatrogenic transmission.

The occupations of affected members in familial CJD were ascertained in less than half of all cases. The distribution is similar to that seen in a larger series of sporadic CJD (Masters *et al.*, 1979*b*). In one family of possible CJD (not included in the present series of 27 families), two affected brothers owned and worked in a butcher shop, in which an affected son also worked. Six unaffected members had little or no contact with the handling of raw meat. Such an occupational situation could be taken as evidence of an environmental source of infection, presumably scrapie-infected sheep products. However, an almost identical occupational history was obtained in one of the families with AD. Here, three affected brothers worked in a butcher shop for twenty-five years, and were known to eat poorly-cooked sheep and beef brains. Three unaffected siblings never worked in the butcher shop. These instances of occupational correlation in both CJD and AD might be coincidental, rather than ætiological.

II. *The Relationship between CJD and Familial AD*

There are several areas in which arguments can be advanced for linking AD and CJD on a common pathogenetic basis. In this section, we analyse data from Groups C and D (*see* Materials and Methods): Group C: the occurrence of definite CJD within families with AD; Group D: the familial occurrence of AD in which one or more members have a clinical syndrome resembling CJD but pathologically have the typical changes of AD. Other areas of research which point to a common pathogenesis of CJD and AD are presented elsewhere: the occurrence of a spectrum of amyloid plaques in the spongiform encephalopathies (Masters *et al.*, 1981); the concurrences of spongiform change and microvacuolation in cases of AD (Flament-Durand and Couck, 1979); the *in vitro* fusion activity demonstrated in the brain tissue of CJD and familial AD (Moreau-Dubois, Brown, Goudsmit, Cathala and

Gajdusek, 1981); and the transmission to primates of an experimental spongiform encephalopathy from two cases of familial AD (Goudsmit, Morrow, Asher, Yanagihara, Masters, Gibbs and Gajdusek, 1980).

The occurrence of proven CJD within families with AD. Among the families with AD referred to our laboratory, there were four families in which one member died from CJD. Two of these families have been published independently (Cook, Ward and Austin, 1979; Ball, 1980). Transmission experiments from brain tissue of affected members in these families are reported in the next section. The occurrence of CJD within families with AD may be coincidental, but seems unlikely given the comparative rarity of both conditions. Although sporadic AD is common, the familial occurrence of AD seems to occur with an incidence similar to familial CJD.

Familial AD, with one or more members with AD who have a clinical syndrome resembling CJD. The clinical evolution of AD may sometimes be rapid (less than three years), with superimposed abnormal movements, especially myoclonus. In this situation the diagnosis of CJD is appropriately raised, to the extent that in our experience AD is the most frequent diagnostic error in all cases of clinically diagnosed CJD. Between 3 and 4 per cent of 1,000 cases of clinically diagnosed CJD referred to our laboratory fall into the diagnostic category of AD after histopathological examination. Among the families with AD under review in this paper, there were 17 families where one or more members presented with a clinical syndrome resembling CJD (Group D, Materials and Methods). There were a total of 88 affected members in the 17 families, 30 of whom had myoclonus or a movement disorder suggesting the possibility of CJD. Affected members in this group, whether having abnormal movements or not, tend to be younger and have a shorter duration of disease than those with the more typical forms of familial AD (compare Table 4 and Table 2). Pathological studies of the brains of cases of AD with clinical features of CJD suggest that the amyloid plaques are more frequent than neurofibrillary change (Masters *et al.*, 1981). If spongiform change were present as well, these cases would have been diagnosed as CJD, and the family placed in Group C. Transmission experiments on the brains of these cases are presented in the next section.

III. *Transmission Experiments in Familial CJD and AD*

We have presented in detail elsewhere some of the data on the results of transmission experiments in laboratory animals inoculated with tissues from cases of familial CJD and AD (Masters *et al.*, 1979*b*; Goudsmit *et al.*, 1980). Virus causing an experimental spongiform encephalopathy in nonhuman primates has been isolated from the brains of 10 cases of CJD occurring within 9 families, and from a further 3 cases of possible familial CJD (not documented in this paper). Additional experiments are in progress on a further 14 cases of familial CJD, but only in 3 cases have the inoculations been on test for more than four years. In 2 of these 3 negative transmissions, the inoculum was brain in tissue culture, a source known to be unpredictable for primary transmission experiments (Asher, Yanagihara, Rogers, Gibbs and Gajdusek, 1979). The only case where the evidence points to a true failure of transmission is Case IV-05 in the Family G.M. Although this patient developed a clinical syndrome consistent with CJD, examination of the brain biopsy failed to show any diagnostic abnormalities. An autopsy was not obtained. Suspensions of the brain biopsy were inoculated by the intracerebral route into two chimpanzees and a squirrel monkey in February 1976. To date, three animals remain alive and well, exceeding by more than two standard deviations the mean incubation periods for primary passage CJD in these species (Goudsmit *et al.*, 1980). One possible explanation for this failed transmission might lie in the fact that the biopsy itself did not show any spongiform change. It is also possible that the patient did not have CJD, although the clinical evidence for CJD was quite convincing. Overall, the rate of isolation of the virus from the brain tissue in familial CJD is therefore 91 per cent (10/11). This is comparable to the isolation rate of 92 per cent (120/130) in sporadic CJD.

In sporadic and/or familial CJD, the virus causing experimental spongiform encephalopathy has been isolated from cerebrospinal fluid, kidney, liver, lung and lymph nodes. The cornea and peripheral blood leukocytes may also be infectious (Duffy *et al.*, 1974; Manuelidis, Angelo, Gorgacz, Kim and Manuelidis, 1977; Manuelidis, Gorgacz and Manuelidis, 1978). To date, virus has not been isolated from the ovary, testis, semen, hair, skin, saliva, fæces, urine, sweat, tears, milk or

TABLE 4. MEAN AGES AT DEATH, DURATIONS OF DISEASE AND SEX RATIOS IN FAMILIES WITH AD WITH ONE OR MORE MEMBERS RESEMBLING CJD

Mean age at death

	No. of cases	*Mean age at death (yrs)*	*SD*	*Range*
All affected members	72	46.1	10.1	25–80
Affected members with myoclonus or other movement disorder	28	47.7	9.5	36–80

Mean duration of disease

	No. of cases	*Mean duration of disease (months)*	*SD*	*Range*
All affected members	55	55.7	31.4	16–168
Affected members with myoclonus or other movement disorder	24	68.2	36.9	24–168

Sex ratio

	No. of males	*No. of females*	*Ratio (M:F)*
All affected members	45	43	1.05

placenta—tissues and secretions which could represent possible modes of transmission in familial CJD. The virus has been transmitted to animals by a variety of routes of inoculation other than intracerebral (intravenous, intramuscular, subcutaneous, intradermal, corneal, and oral), but the oral route was achieved only after high doses with the probability of self-inoculation into open wounds, mucosal defects or conjunctiva (Gibbs, Amyx, Bacote, Masters and Gajdusek, 1980). These studies, therefore, have not provided a ready answer as to how the virus may be passaged between family members. The failure to isolate virus in ovary, testis or semen, or from various body secretions may only reflect the insensitivity of the bio-assay system to low doses of virus. In the absence of vertical transmission, it is not difficult to envisage many different possible portals of entry for the virus, based on the effective routes of inoculation listed above.

Because of the similarities between CJD and AD (Sections I, II), priority was given to the inoculation of brain tissue from cases of AD into nonhuman primates shortly after the transmissibility of CJD was discovered. Since 1968, brain tissue from 52 cases of AD (sporadic and familial) has been inoculated intracerebrally into nonhuman primates; 18 of these were familial cases. In two cases of familial AD, brain tissue inoculated into nonhuman primates caused a spongiform encephalopathy. All attempts to reproduce these results by re-inoculation of the original material to date have failed (Goudsmit *et al.*, 1980). Seventeen other cases of AD (4 familial, 13 sporadic) have been inoculated in nonhuman primates for more than four years, without causing disease.

In the category of familial AD, with one or more members affected with CJD (Group C, Materials and Methods), brain tissue inoculated from one case of AD has not been on test for a sufficient period of time. However, brain tissue from a case diagnosed as CJD in a family with AD has caused a spongiform encephalopathy in a squirrel monkey. The clinical presentation, pathology and the experimental transmission are somewhat atypical. The propositus (Family A.G.L., kindly referred by Professor J. Ulrich, University of Basel) died in 1976, aged 57 years, after a three-year history of progressive memory loss, dysphasia, spasticity, and occasional epileptic convulsions. Autopsy showed cerebral atrophy, and microscopically there was severe neuronal loss and gliosis in the hippocampus and subiculum. The superficial layers of the cerebral cortex had pronounced vacuolation, without significant gliosis or neuronal loss, and not typical of the usual spongiform change seen in CJD. At the time of necropsy, the whole brain was fixed in formalin, but two months later some of the fixed brain was frozen and prepared for inoculation into squirrel monkeys and dilutions ranging from 10-1 to 10-4. The monkey inoculated with the 10-4 suspension developed a typical spongiform encephalopathy thirty-five months after inoculation; the remaining four animals inoculated with higher doses of brain remain unaffected. Two sisters of the propositus died from dementing illnesses, and an autopsy performed on one sister showed extensive senile (neuritic) plaque deposition, congophilic angiopathy, but no spongiform change or neurofibrillary degeneration. Clinically and pathologically, the propositus did not fulfil the complete criteria for the diagnosis of CJD, and must be considered atypical. The isolation of virus from the formalin-fixed brain only at high dilution is difficult to explain, but is not inconsistent with its known resistance to inactivation by formaldehyde (Gajdusek, Gibbs, Collins and Traub, 1976), or the scattered 'takes' we have observed with inocula of low infectivity.

Finally, brain tissue from seven affected members in families with AD where the clinical evolution suggested a diagnosis of CJD (Group D, Section II), has been inoculated into nonhuman primates. In only two cases have the inoculations been on test for a sufficient period of time for them to be considered negative.

DISCUSSION

The familial occurrence of CJD, with transmission through several generations as an autosomal dominant trait, presents an opportunity to examine the natural mechanism of spread of the virus. In this context, two modes of vertical transmission should be considered. First, genomic integration of the virus with transmission through either the sperm or ovum; secondly, infection occurring *in utero* or in the post-natal period either through contact with an affected parent or some other source of infection. All mechanisms postulated for the mode of transmission of sporadic CJD (Gajdusek, 1977; Masters *et al.*, 1979*b*) must also be considered, with constraints added to explain the familial aggregation of cases. These include an inherited susceptibility to infection or a common environmental source of infection.

The earlier age at onset and death in familial compared to sporadic CJD suggests an earlier age of exposure to the virus, assuming rather uniform incubation periods. This difference in age, however, could also be produced by a genetically determined susceptibility to infection. The absence of any maternal effect argues strongly against a transplacental, breast milk, or other paranatal route of maternal vertical transmission.

The analysis of temporal and spatial separations between affected parents and children demonstrates that incubation periods ranging at least from one to four decades are to be expected, whether transmission is occurring laterally or vertically. The most illustrative family was reported by Guidon (1978), in which affected siblings were separated in infancy. International and transcontinental migrations of affected families suggests that environmental sources of common exposure are unlikely. The observation that affected siblings tend to die at the same age, and not at the same time, is more consistent with some form of vertical transmission (including infection in the first months of life) rather than a common environmental point exposure to infection, assuming again rather uniform incubation periods. CJD occurred in four families in members related by marriage, which is strong evidence in favour of lateral or common source transmission in occasional cases, although it is even more remarkable that so few conjugal cases have occurred.

Observations on naturally occurring kuru in Papua New Guinea, scrapie in sheep and goats, together with the data derived from the experimental models of the spongiform encephalopathies are relevant to the mechanisms of transmission of familial CJD.

There is compelling evidence that vertical transmission, in any form, does not occur in human kuru or in any of the experimental infections with CJD, kuru or scrapie. Not one of several hundred infants born since 1956 to kuru-affected mothers has developed the disease (Gajdusek, 1977). Of course, it remains possible that the incubation period for natural kuru with portals of entry other than those occasioned by contamination from ritual cannabalism is closer to four decades rather than two. In this case, kuru might yet still occur in these orphans decades from now, but it could not account for the large numbers of prepubertal patients seen over twenty years ago. Vertical transmission has also not been seen in our animal colonies (Amyx, Gibbs, Gajdusek and Greer, 1981), nor in the guinea pig model of CJD (Manuelidis and Manuelidis, 1979). There is good evidence, however, for a maternal effect in the development of natural scrapie (Hourrigan, Klingsporn, Clark and de Camp, 1979). Equally important from the studies of the epidemiology of natural scrapie are the observations that infection tends to be acquired within the first six months of life (Hourrigan *et al.*, 1979), possibly through the alimentary tract (Hadlow, Race, Kennedy and Eklund, 1979).

The genetic control over expression of disease in experimental scrapie has been repeatedly documented by Dickinson (Dickinson and Fraser, 1979), where a complex interaction between the strain of scrapie virus and a gene with two alleles controlling incubation period has emerged. The situation in the genetic control of natural scrapie infection of sheep, however, remains to be determined. While differing breeds of sheep have vastly different susceptibilities or resistance to natural and experimental scrapie infection, the precise nature of the genetic control is disputed (Dickinson and Fraser, 1979; Kimberlin, 1979; Parry, 1979*a*, *b*). In spite of extensive studies in the kuru region, genetically inherited factors associated with the disease have not been discovered, with the exception of the association of kuru with the Gc Ab-Ab phenotype (Kitchin, Bearn, Alpers and Gajdusek, 1972; Wiesenfeld and Gajdusek, 1975). Even in this example, the association may not be relevant to the disease (Weisenfeld and Gajdusek, 1975). Segregation of histocompatibility antigens was not found in the only family with CJD to be examined to date (the O.S. family—Kovanen, Tiilikainen and Haltia, 1980), but at least seven of eight affected members in this family shared the HLA antigens A28 and B8. Segregation of HLA or other chromosome-6 markers was not found in one family with AD (Goudsmit, White, Weitkamp, Keats, Morrow and Gajdusek, 1981).

Experimental studies have shown the presence of the scrapie virus in the placenta (Dickinson and Fraser, 1979), and the CJD virus in cornea and blood, but to date none of the viruses in this group has been consistently demonstrated in testis, ovary, semen, urine, fæces, milk, saliva or other peripheral tissues or secretions which could explain the portal of exit or mode of transmission for either vertical or horizontal transmission. While most routes of inoculation have been shown to be effective in the experimental disease, the only known mechanism of transmission of human CJD has been through iatrogenic parenteral inoculation (Masters *et al.*, 1979*b*).

The possibility that AD shares a common pathogenesis with CJD has been emphasized in this paper. The evidence to date, however, is only suggestive, and until further evidence accrues, it seems prudent for practical purposes to regard AD as non-infectious.

The epidemiology of the disappearance of kuru indicates that there is no vertical transmission of the virus, and no communicability in the absence of contamination with infective internal tissues. Furthermore, it indicates that there is no extra-human reservoir or vector for transmission of the virus. Kuru causing a large proportion of all adult female deaths in the villages of highest involvement for over a decade suggests little or no genetic resistance to infection in man. The familial occurrence of CJD, however, suggests the contrary: either a genetic susceptibility to infection from the virus or some form of vertical transmission. The data presented in this study are quite consistent with an hypothesis invoking both mechanisms, where a genetically susceptible individual is infected in early infancy or childhood from a subclinically or clinically affected parent, a mechanism that is also consistent with the more recent data on the natural mode of transmission of natural scrapie. The paradox provided by the epidemiological studies of familial CJD and of kuru is unresolved, but in its resolution will surely lie valuable new information about the pathogenesis and natural history of both diseases.

SUMMARY

We have analysed the familial occurrence of Creutzfeldt-Jakob disease (CJD) in 27 families selected from a total of 73 families. Fifteen per cent of all cases of CJD have a family history of disease consistent with autosomal dominant transmission. The onset of disease in familial cases is significantly earlier than in sporadic cases. A maternal effect was not found, nor was there evidence for prenatal vertical transmission of the virus. Temporal and spatial separations between affected members demonstrates that incubation periods ranging at least from one to four decades are to be expected. Affected siblings tend to die at the same age, and not at the same time, which is consistent with some form of vertical transmission (either prenatal or early postnatal), assuming rather uniform incubation periods. CJD occurred in four families in members related by marriage, evidence in favour of horizontal or common source transmission in occasional cases.

The familial occurrence of CJD and Alzheimer's disease (AD) were compared using data on 52 families with AD. The age at death and duration of disease in familial AD is greater than in familial CJD. Familial AD also occurs in a pattern of autosomal dominant transmission, without maternal effect. There were four

families with AD in which one or more members died from CJD. There were an additional 17 families with AD in which one or more members presented with clinical features resembling CJD. Although virus causing an experimental spongiform encephalopathy was isolated from the brain of two cases of familial AD, most cases of sporadic and familial AD tested failed to cause disease when brain tissue was inoculated into nonhuman primates.

The precise mechanism of spread of the virus in familial CJD remains unknown. The results of the present study are consistent with the hypothesis of a genetically inherited susceptibility to infection which is acquired in early infancy or childhood. Other proposed mechanisms such as prenatal vertical transmission or a common environmental source of infection seem less likely.

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(*Received July 22, 1980*)

Brain (1981), **104**, 559–588

CREUTZFELDT-JAKOB DISEASE VIRUS ISOLATIONS FROM THE GERSTMANN-STRÄUSSLER SYNDROME

WITH AN ANALYSIS OF THE VARIOUS FORMS OF AMYLOID PLAQUE DEPOSITION IN THE VIRUS-INDUCED SPONGIFORM ENCEPHALOPATHIES

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INTRODUCTION

FOUR patients brought to our attention as atypical Creutzfeldt-Jakob disease (CJD), whose brain when inoculated into nonhuman primates caused an experimental spongiform encephalopathy, have shown on retrospective analysis many of the clinical and pathological features of the Gerstmann-Sträussler syndrome (GSS), also known as Sträussler's disease or 'spinocerebellar ataxia with dementia and plaque-like deposits' (Vinken and Bruyn, 1975), and Gerstmann-Sträussler-Scheinker's disease (Schlote, Boellaard, Schumm and Stöhr, 1980). To emphasize the syndromic nature of this probable heterogeneous disorder, we have elected to use the term Gerstmann-Sträussler syndrome until the nosology has been clarified. In this paper we investigate the possibility that a variant strain of the CJD virus may be a cause of the GSS by reference to a series of 7 cases of this syndrome referred to our laboratory as atypical CJD, and 10 other cases reported in the literature.

One distinctive feature of the GSS is the deposition of large numbers of unusual forms of amyloid plaques throughout the brain, which on first inspection would be classified in an intermediate position between the amyloid senile plaque (SP) of Alzheimer's disease (AD) (Wiśniewski and Terry, 1973) and the kuru plaque (KP) of kuru, CJD, and natural and experimental scrapie (Klatzo, Gajdusek and Zigas, 1959; Chou and Martin, 1971; Beck, Daniel and Parry, 1964; Field, Raine and Joyce, 1967; Bruce and Fraser, 1975; Bruce, Dickinson and Fraser, 1976). There is considerable disagreement among neuropathologists over the classification of KP and SP: on the one hand are those who believe that the KP is closely related to the amyloid SP, and on the other are those who emphasize the differences in morphology, and by implication, in pathogenesis. In this paper, we also review a large series of patients with spongiform encephalopathies who have KP or SP, and discuss the pathogenesis of the plaques. The evidence suggests that KP, SP and the amyloid plaques of the GSS have a common pathogenesis, and that their differing morphologies may be related to the temporal sequence in which the amyloid is deposited, reflected in the different durations of disease in each group. These observations are discussed in relation to pathogenesis of the amyloid plaque of AD.

Since the GSS, a form of cerebellar ataxia with dementia and amyloid plaques, is not well described in the English literature, we first present the historical background, and a review of selected published cases which fit this syndrome (Table 1).

HISTORICAL BACKGROUND

Gerstmann's Original Descriptions of the 'H' family as 'A Peculiar Heredofamilial Disease of the Central Nervous System. A Contribution to the Problem of Premature Local Aging'

Gerstmann (1928) described the clinical features of a female with an unusual cerebellar disease, drawing attention to a previously undescribed reflex phenomenon: when the patient's arms were extended, turning of the head caused the arms to cross in the midline, contralateral arm above the ipsilateral arm with respect to the side of head movement. The detailed clinical and pathological features of this case, together with the family history of seven other affected members, were subsequently described by Gerstmann, Sträussler and Scheinker (1936). The disease of the propositus (Case 1, Table 1) began rather abruptly at the age of 25 years, with disturbed equilibrium, ataxia, slurred speech and mental changes (irritability and impairment of intellect). When examined one year after the onset, cerebellar signs and dementia were evident. The course of the illness had been relapsing rather than chronic and progressive. The main clinical signs were ataxia, intention tremor, hypotonia, dysarthria, dysdiadokokinesis and inability to walk. There was a pseudobulbar disturbance of swallowing. Lateral and upward gaze nystagmus were seen, and there was impaired convergence, with severe limitation of upward gaze. Reflexes were diminished, but bilateral Babinski responses were present. She died six years after the onset of illness.

The pathological finding emphasized was 'an elective degeneration of the system of the dentate nuclei and brachia conjunctiva'. In the spinal cord, there was a loss of cells in Clarke's column with degeneration of the lateral and dorsal spinocerebellar tracts, corticospinal tracts, and to a lesser extent of the dorsal columns. Corticospinal fibre loss was evident at the level of both the pons and medulla. There was a severe loss of cells in the dentate nuclei, with a loss of myelin in the middle and superior cerebellar peduncles and in most areas of the cerebellum itself. Purkinje cells were normal, but there were occasional torpedos, and the granule cells were depleted. In all layers of the cerebellum, especially the molecular layer, there were 'peculiar inclusions of a foreign substance'. In the Nissl preparation, these inclusions were grouped around a bluish green nucleus, and were round, irregular or jagged, forming spheres and clumps. Occasionally at the periphery, there were glial elements resembling those seen in senile plaques, but more frequently, the substance was deposited in the neuropil without cellular reaction. 'These formations are shapes that are rarely found among the senile plaque forms'. These argyrophilic plaques were also seen throughout the cerebrum and brain-stem. In the cerebrum 'the substance that forms the substrate of the plaques was found in small and larger spheres in vessels, some of them attached to the interior walls, some of them free in the lumen'. In the cerebral cortex, gliosis was present, and 'the second and third cell layers show holes [Lücken], as a result of which the architectonics appear to be markedly disturbed'.

TABLE 1. SUMMARY OF CASES OF THE GERSTMANN-STRÄUSSLER SYNDROME REPORTED IN THE LITERATURE

Identification and references	*Country of origin*	*Sex age (yrs)*	*Duration (months)*	*Chief symptoms and signs in order of appearance*	*Pathological findings in brain*	*Location of plaques*
1. Gerstmann, 1928; Gerstmann *et al.*, 1936	Germany	F 31	72	1. Ataxia 2. Dysarthria 3. Dementia 4. Nystagmus 5. Limitation of upward gaze 6. Hyporeflexia but bilat extensor plantar responses (17 other affected members in 4 generations; 4 studied pathologically with similar findings)	Possible spongiform change-vacuoles [Lücken] and gliosis in cerebral cortex Degeneration of dentate nuclei and branchia conjunctiva Degeneration of spinocerebellar and corticospinal tracts Loss of white matter in cerebellum, and loss of granule cells	Cerebellum Cerebrum Brain-stem
2. Worster-Drought *et al.*, 1933, 1940, 1944 (Case 1, C.G., propositus)	UK	M 54	96	1 Memory loss 2. Dysarthria 3. Hyperrelexia 4. Dementia 5. Spastic gait	Loss of white matter in cerebral hemispheres Purkinje cell loss Small vascular inclusions and hyaline thickening Possible amyloid angiopathy Few tangles in hippocampus No spongiform change	Hippocampus Cerebellum
3. Worster-Drought *et al*, 1933, 1940, 1944 (Case 2, M.B., sister of Case 1)	UK	F 52	108	1. Memory loss 2. Hyperreflexia 3. Dysparthria 4. Ataxia 5. Dementia 6. Nystagmus (8 other members of family affected)	Similar to Case 1, some vessels occluded by hyaline change	Hippocampus Cerebellum Brain-stem
4. Stengel and Wilson, 1946 (Case 1)	Scotland	M 49	22	1. Somnulence 2 Dementia 3. Ataxia 4. Fasciculations, atrophy 5. Posterior column signs 6 Absent reflexes in lower limbs with bilat. extensor plantar responses 7. Limitation of upward gaze 8. Bulbar palsy	Focal neuronal loss and gliosis in cerebral cortex, caudate and putamen Foci of white matter loss in cerebral hemispheres and cerebellum Loss of white matter in posterior and lateral columns of cord, with loss of motor neurons in cord	Cerebral cortex
5. Crémieux *et al.*, 1963	France	M 62	30	1. Ataxia 2. Hyporeflexia 3. Dementia 4. Rigidity (Sister also affected)	Possible spongiform change Loss of white matter in posterior columns, corticospinal tract Few neurofibrillary tangles in cerebral cortex Neuronal loss and gliosis in cerebral cortex, striatum and thalamus Loss of Purkinje cell	Cerebral cortex Cerebellum
6. Stam *et al.*, 1968	The Netherlands	M 36	36 (approx.)	1. Dementia 2. Rigidity and tremor 3. Myoclonus	Spongiform encephalopathy	Cerebral cortex Striatum Cerebellum
7. Matsuoka *et al.*, 1970 (Case 2)	Japan	M 35	21	1. Ataxia 2. Hemiparesis 3. Dementia	Spongiform encephalopathy Loss of myelin in corticospinal and spinocerebellar tracts	Cerebral cortex Striatum Cerebellum
8. Nakashima *et al.*, 1976	Japan	M 56	132	1. Ataxia 2. Paræthesia 3. Bulbar palsy 4. Fasciculations 5. Dementia (Father and sister died with a similar disease)	Spongiform encephalopathy Widespread loss of myelin	Cerebellum Striatum Brain-stem Subcortical white matter
9. Nakamura *et al.*, 1979	Japan	M 49	66	1. Ataxia 2. Paræsthesia in legs 3. Nystagmus and dysarthria 4. Loss of reflexes in legs 5. Dementia 6. Pyramidal signs 7. Rigidity 8. Atrophy and fasciculations 9. Myoclonus (3 of 6 siblings have progressive cerebellar ataxia since childhood)	Spongiform encephalopathy Moderate loss of neurons in anterior horns and loss of white matter in corticospinal and spinocerebellar tracts	Cerebral cortex Striatum Cerebellum
10. Boellaard and Schlote, 1980 (Case 2)	W. Germany	F 56	54	1. Ataxia 2. Paræsthesia in legs 3. Dysarthria 4. Dementia 5. Loss of leg reflexes with extensor plantar responses (Similar disease in 3 members of family in 3 generations)	Spongiform encephalopathy Moderate loss of anterior horn cells	Cerebral cortex Striatum Cerebellum

In discussion, the authors concluded that their case was unique, while sharing many of the clinicopathological features of the spinocerebellar degenerations (Friedreich), cerebellar degenerations (Marie), and dentatorubral degenerations (Ramsay Hunt). With regard to the plaque deposition, the authors were without doubt that it differed from the usual senile plaque of Alzheimer's disease, although they believed it was probably closely related in pathogenesis. They drew attention to the report of Barrett (1913) who reported the case of a female dying at the age of 37 years from a disease characterized by dementia, myoclonus, ataxia and spasticity, of four years' duration. In addition to severe corticospinal tract degeneration, there were prominent neurofibrillary changes and a severe deposition of senile plaques throughout the brain, including the cerebellum. The family history of this patient was not described, but Gerstmann suggested that it represented a link in a spectrum between the diseases he had described and Alzheimer's disease.

The authors also emphasized the possible vascular origin of the plaque material, as seen within the lumen of cerebral blood vessels of the patient. They did not discuss the significance of the vacuoles, holes or lacunes [Lücken] in the cortical grey matter, which in retrospect may have some bearing on the relationship of this disease to the spongiform encephalopathies. As in the original reports of Creutzfeldt (1920) and Jakob (1923), it is impossible to determine from the photomicrographs published whether a pathognomonic spongiform change or some other form of vacuolation occurred (Masters and Richardson, 1978).

Subsequently, four other affected members of the 'H' family died, and were studied by von Braunmühl (1954) and Seitelberger (1962). From the data available on four affected members, the mean age at death of affected members in the family was 46 years, and the mean duration of disease was six years (range four to seven years). All presented similar clinical and pathological findings, with the exception that the degenerative changes seen in the dentate nuclei and brachia conjunctiva of Gerstmann's case were not as pronounced in the four other cases. Seitelberger (1962) inferred that this familial disease was closely related to kuru, based on his own personal observations and those of Klatzo *et al.* (1959) and Hadlow (1959). At that time, the nature of the spongiform change in kuru was not appreciated, nor was the transmissibility of the disease known.

The 'CG' Family of Worster-Drought

The family described by Worster-Drought (Worster-Drought, Hill and McMenemey, 1933; Robertson, 1934; Worster-Drought, Greenfield and McMenemey 1940, 1944) was originally classified as a type of spastic pseudosclerosis of the Creutzfeldt-Jakob type by Kinnier Wilson (1940). When pathological data became available, it was clear that there was little resemblance to CJD (Worster-Drought *et al.*, 1940). However, in the context of the GSS, there are striking pathological similarities (Cases 2, 3 in Table 1). Of the eleven affected members in this family, all presented a similar picture of a progressive spastic paralysis with dementia. The mean age at death was 55 years, and the mean duration of disease was nine years (range two to eighteen years). Cerebellar signs were not prominent, the ataxia being ascribed largely to pyramidal involvement. Two affected members were examined pathologically. Many small blood vessels in the brain and meninges showed a hyaline thickening with extrusion of an amorphous substance into the perivascular spaces and into the brain parenchyma. Scattered throughout the hippocampus and cerebellum, this material formed 'plaque-like structures', occasionally resembling senile plaques. Neurofibrillary change, possibly consistent with the patients' ages, was also seen in the hippocampus. The numbers of Purkinje cells were considerably reduced and some showed torpedos. The white matter of the cerebral hemispheres was pale in the myelin stains, and there was a severe gliosis in the corpus callosum. Some of these plaques were seen in the anterior horns of the spinal cord. The striatum, thalamus and brain-stem were normal. The authors concluded that the vascular changes may have caused the loss of myelin in the cerebral hemispheres, and in turn caused the spastic paralysis. The plaque-like structures, which could not be correlated with the vascular changes, were believed to have caused the dementing process and it was suggested that the 'ataxia is related in some degree to the pathological changes in the cerebellum'. In retrospect, while certain differences exist between this family and that described by Gerstmann (lack of cerebellar signs and no tract degeneration in the spinal cord), it is clear that the underlying pathological process is very similar.

Other Cases, Sporadic and Familial, which Resemble the GSS

Other cases of familial progressive spastic paresis with dementia and amyloid plaque deposition were described about the same time (Marinesco, 1931; van Bogaert, Maere and de Smedt, 1940; Lüers, 1947/48; Corsellis and Brierley, 1954), and may also represent variants of the GSS. The type of amyloid deposition in the cases of Corsellis and Brierley (1954) closely resembles that in Gerstmann's cases. The case of Stengel and Wilson (1946) could be placed within the GSS (Case 4 in Table 1). Spongiform change, if present, was not described.

Crémieux, Recordier, Boudouresques, Roger, Toga, Daniel and Dubois (1963) described a patient with a familial spinocerebellar ataxia and dementia (Case 5, Table 1). Aged 62 years at death from a disease lasting two and a half years, this patient developed an extrapyramidal rigidity in addition to cerebellar signs, hyporeflexia and dementia. In the spinal cord, there was degeneration of the posterior columns, and some loss of myelin in the pyramidal tracts at the level of their decussation. There was gliosis of the olivary nuclei with some loss of Purkinje cells. Throughout the molecular layer of the cerebellum, senile plaques were found. In the frontal and temporal cortex, caudate and thalamus, neuronal loss and gliosis were evident, together with a spongiform change [état spongieux diffus microvacuolaire] predominantly in the superficial layers. Many senile plaques and occasional neurofibrillary tangles were seen. From the authors' descriptions and photomicrographs, it is not clear whether the plaques were typical of those seen in Alzheimer's disease, or resembled the plaques described by Gerstmann *et al.* (1936); nor is it possible to distinguish between status spongiosus and spongiform change (Masters and Richardson, 1978), although the authors noted the resemblance of this change to the subacute spongiform encephalopathy described by Nevin, McMenemy, Behrman and Jones (1960).

There have been at least 13 case reports since 1968 of chronic encephalopathies, most with spongiform change, with abundant amyloid plaque deposition resembling that seen in the GSS (Stam, Wigboldus and Grosveld, 1968; Matsuoka, Hamanaka, Taii, Tatebayashi, Kijima and Nishikawa, 1970; Boudouresques, Toga, Khalil, Ali Chérif, Pellissier and Gosset, 1976; Nakashima, Makino, Kinoshita and Yagashita, 1976; Rosenthal, Keesey, Crandall and Brown, 1976; Hirano, Tsuchiyama, Kawai and Mori, 1977; Kuroda, Morisada, Tateishi, Fukui and Hosokawa, 1977; Motomura, Yamashita, Kawanami, Ohta and Kuroiwa, 1977; Ohta, Koga, Tateishi, Motomura, Yamashita, Kawanami, Oda and Kuroiwa, 1978; Tateishi, Koga, Ohta, and Sato, 1979; Tateishi, Ohta, Koga, Sato and Kuroiwa, 1979; Tateishi, Sato, Koga, Ohta and Kuroiwa, 1979; Nakamura, Takamatsu, Shida, Kotorii, Anraku and Kida, 1979; Shaw, 1979; Tateishi, Koga, Sato and Mori, 1980; Boellaard and Schlote, 1980). Illustrative cases from these are summarized in Table 1 (Cases 6 to 9). Most cases have had prominent cerebellar signs, and the over-represented reports from Japan have drawn attention to a degenerative state in the white matter which exceeds that expected for the degree of neuronal loss. Indeed, Tateishi's experiments (Tateishi, Koga, Ohta and Sato, 1979, confirmed in our laboratory), have shown that the virus causing the disease in his patient induced white matter changes in experimentally-infected rodents. Moreover, the incubation period for this virus isolate was remarkably short.

Most recently, Boellaard and Schlote (1980) described two families in which the typical features of the GSS occurred, together with changes of a spongiform encephalopathy. In the first family ('Sch'), there were 13 affected members, mean age at death 49 years, with a mean duration of illness four years (range three to five years). The propositus, aged 47 years at death, began a five-year illness with an acute onset of ataxia, dysarthria and paræsthesia in the legs. A rapidly progressive dementia appeared two years after the onset, when cerebellar signs were prominent. Terminally, hypertonia and rigidity developed. When examined, the brain showed a widespread loss of neurons and gliosis in the cerebral cortex with sparing of the hippocampus. A spongiform change was described as prominent in the temporal and occipital regions. The anterior nuclear group of the thalamus also showed neuronal loss and gliosis. Many amyloid plaques, of varying morphology, were seen throughout the cortex, thalamus and cerebellum. In the cerebellum, there was a moderate loss of Purkinje cells, a more severe loss of granule cells, and loss of myelin and gliosis in the white matter. Neuronal loss was also evident in the dentate nuclei, inferior olivary nuclei and anterior horns of the spinal cord. Pallor of the corticospinal and spinocerebellar tracts was found in both the lower brain-stem and spinal cord. Brain tissue from another affected member in this family has become available for experimental transmission studies (Case 5, Table 2, *see* Results).

In the second ('F') family of Boellaard and Schlote (1980), there were four affected members dying at a mean age of 49 years, of a disease with mean duration of five years (Case 10, Table 1). The propositus had a slowly progressive flaccid paralysis of the legs, followed by dementia. The illness lasted four and a half years. Amyloid plaques, of a similar varied morphology as in the first family, were found in the cerebral cortex, striatum and cerebellum. Spongiform change was seen in the superficial layers of the cerebral cortex. No corticospinal or spinocerebellar tract degeneration was seen.

MATERIALS AND METHODS

Cases analysed in this paper were selected from our records on more than 1,200 patients with CJD referred to the Laboratory of Central Nervous System Studies since 1968, and from reports of approximately 600 cases of CJD published in the literature. All cases with any type of amyloid plaque deposition in the brain were reviewed, and divided into three groups on the basis of the clinical and pathological findings: Group 1: cases resembling the Gerstmann-Sträussler syndrome; Group 2: cases of spongiform encephalopathy with kuru plaques; Group 3: cases of spongiform encephalopathy with senile plaques. We excluded from consideration a group of 54 patients referred to our laboratory with the syndrome of the amyotrophic form of CJD, some of whom have senile plaques and neurofibrillary tangles in addition to the pathological changes of amyotrophic lateral sclerosis, and have proven not to be transmissible by inoculation of brain tissue into nonhuman primates (Salazar, Masters, Gajdusek and Gibbs, 1981). The cases in each of the above three groups were compared with a series of 97 cases of pathologically confirmed spongiform encephalopathies (CJD), without amyloid plaque deposition, and from which a virus causing an experimental spongiform encephalopathy was isolated in nonhuman primates (Bernoulli, Masters, Gajdusek, Gibbs and Harris, 1979; Masters, Harris, Gajdusek, Gibbs, Bernoulli and Asher, 1979). The experimental procedures used in the inoculation of nonhuman primates were performed using methods previously described (Gajdusek, Gibbs and Alpers, 1966).

This review of the case records of all patients referred to our laboratory as typical or atypical CJD resulted in the identification of 34 cases with some form of amyloid plaque deposition in the brain, among nearly 400 cases where adequate neuropathological data were available. A further 28 cases of CJD with amyloid plaques were reported in the literature.

The composition of Groups 1, 2 and 3, and the criteria used for their classification, are summarized below.

Group 1. Cases Resembling the Gerstmann-Sträussler Syndrome

Seven cases were identified in which the amyloid plaque deposition resembled that described in the GSS, in that there was a widespread deposition of irregular masses of amyloid in the parenchyma, largely without surrounding gliosis or neuritic degeneration. These included 6 cases published in the literature from which brain specimens were sent to our laboratory for transmission experiments, and on which we have additional unpublished data (*see* Table 2). Brain tissue from 3 of these 7 cases has caused a spongiform encephalopathy when inoculated into nonhuman primates. Together with these 7 referred cases, we combined data from 10 cases published in the literature (Table 1), chiefly for the purpose of analysis of the mean age at death and durations of disease.

Group 2. Spongiform Encephalopathy with Kuru Plaques

Kuru plaques were defined as round to ovoid deposits having a central core of amyloid radially surrounded by delicate fibrillary processes. Twenty-three cases of CJD with KP were identified, comprising 14 cases referred to our laboratory (which include 5 published cases), and 9 published cases. Brain tissue from 3 cases of CJD with KP have caused spongiform encephalopathies when inoculated into nonhuman primates.

The cases in his group were also compared with a series of 38 cases of human kuru in which neuropathological data are available. Although more than 80 cases of human kuru have undergone necropsy, we have access to pathological reports on 57 cases (12 cases of Klatzo *et al.*, 1959; 5 cases of Fowler and Robertson, 1959; 3 cases of Neumann, Gajdusek and Zigas, 1964; 2 cases of Kakulas, Lecours and Gajdusek, 1967; 14 cases of Anderson, 1968, 1970; 4 cases of Field, Mathews and Raine, 1969; 13 unpublished cases of E. Beck and P. M. Daniel, personal communication; 1 unpublished case of K. Earle, personal communication; 3 unpublished cases of C. Masters, T. Smith, D. E. Gajdusek and M. Alpers). In 19 of these 57 cases, either the presence or absence of KP was not determined (Fowler and Robertson, 1959), or the cases with and without KP were not individually identified, leaving 38 cases for the present analysis.

Group 3. Cases of Spongiform Encephalopathy with Senile Plaques

Included in this group were all cases of CJD with typical clinical evolution of disease, confirmed pathologically as having a spongiform encephalopathy, and showing senile plaques in any area of the brain. These plaques include the neuritic type ('primitive' or 'classic') or the amyloid ('compact') type as defined by Wiśniewski and Terry (1973). Some forms of this latter type of amyloid plaque closely resemble the plaque of the GSS, and therefore cases of CJD were included in this category only if mixtures of both neuritic and amyloid plaques were seen. Twenty-two cases fell into this category, 13 cases referred to our laboratory and 9 cases published by other workers. Brain tissue from 5 of these referred cases has caused a spongiform encephalopathy when inoculated into nonhuman primates.

RESULTS

There was a total of 62 cases of CJD with some form of amyloid plaque deposition in the brain, among nearly 1,000 cases where neuropathological data were available. A better estimate of the incidence of amyloid plaques in CJD was obtained from the detailed pathological examination of 107 cases where brain tissue inoculated into nonhuman primates resulted in experimental spongiform encephalopathies. In this transmissible group, there were 7 cases (9 per cent) with some form of amyloid plaque deposition. These 62 cases are divided into three groups on the basis of the morphology of the amyloid plaque deposition: 17 cases which resemble the GSS; 23 cases with KP; and 22 cases with SP. Below, we describe these three groups of patients, comparing the clinical and pathological findings, mean ages at death and durations of disease, and transmissibility in each of these groups with a series of 97 cases of transmissible CJD without brain amyloid deposition.

TABLE 2. INNOCULATION OF ANIMALS AND TRANSMISSIONS FROM BRAIN SPECIMENS FROM PATIENTS WITH THE GERSTMANN-STRÄUSSLER SYNDROME

Identification and references	*Country of origin*	*Sex age (yrs)*	*Duration (months)*	*Chief symptoms and signs in order of appearance*	*Pathological findings in brain*	*Location of plaques*	*Experimental data*
1. (K.F.) Tateishi, Koga *et al.*, 1979; Ohta *et al.*, 1978; Motomura *et al.*, 1977	Japan	M 56	47	1. Paraesthesia in legs 2. Ataxia 3. Dementia 4. Apraxia 5. Rigidity 6. Myoclonus (transient)	Spongiform encephalopathy Loss of white matter in cerebral hemispheres, cerebellum, corticospinal and spinocerebellar tracts, and basis pontis	Cerebral cortex Cerebellum Thalamus Amygdala Hippocampus	Virus isolated in mice, rats and guinea pigs with short incubation in mice; white matter also involved in rodent transmissions. Virus isolated in squirrel monkey with usual incubation period and pathology
2. (Y.M.) Hirano *et al.*, 1977	Japan	F 29	51	1. Ataxia 2. Dysarthria 3. Dementia 4. Pyramidal signs 5. Myoclonus 6. Rigidity	Spongiform encephalopathy Loss of white matter in cerebellum, cerebrum, brain-stem, corticospinal and spinocerebellar tracts	Cerebral cortex Cerebellum	Virus isolated in spider monkey 13.5 months after inoculation
3. (J.C.M.)	France	M 39	105	1. Ataxia 2. Dementia 3. Rigidity 4. Apraxia 5. Aphasia (Father died aged 46 yrs with similar illness)	Loss of Purkinje cells and gliosis in cerebellum No spongiform change	Cerebellum	On test, April 1979
4. (Po.) Boudouresques *et al.*, 1976	France	M 50	48	1. Ataxia 2. Dysarthria 3. Hyporeflexia of lower limbs but bilat. extensor plantar responses 4. Atrophy and fasciculations in legs 5. Extrapyramidal signs 6. Parinaud syndrome (Mental state not ascertained because of anarthria)	Loss of myelin in cerebellum, superior cerebellar peduncles, corticospinal, dorsal and ventral spinocerebellar traits, globus pallidus, subthalamic nucleus Loss of neurons in globus pallidus, subthalamic nucleus, granular layer of cerebellum, anterior horns of spinal cord No spongiform changes	Cerebral cortex Cerebellum Thalamus	On test, formalin-fixed brain, May 1977
5. (E.S.) Boellaard and Schlote, 1980	W. Germany	M 59	50	1. Ataxia 2. Dysarthria, nystagmus 3. Dementia 4. Decreased hearing and vision 5. Amyotrophy 6. Vertical gaze paresis 7. Decreased reflexes in lower limbs with bilat. extensor plantar responses (This is Case III-2 of 'Sch' family in which 12 other members had similar neurological diseases. Sister (III-4) had probable spongiform encephalopathy)	Loss of nerve cells in dentate nucleus and cerebral cortex No spongiform change Mild gliosis in cerebral white matter	Cerebral cortex Cerebellum Thalamus Midbrain White matter of cerebrum and cerebellum	On test, April 1979
6. (J.W.) (Case III-9 in fig. 1) Mishra, 1974; Rosenthal *et al.*, 1976; Adams *et al.*, 1979	USA/UK	M 42	13	1. Headache, visual disturbance 2. Ataxia 3. Confusion 4. Dementia 5. Myoclonus 6. Rigidity 7. Pyramidal signs (Large family history with 17 other affected members)	Spongiform encephalopathy	Cerebral cortex Cerebellum Hippocampus	Virus isolated in spider and squirrel monkeys up to dilutions of 10^{-3} Chimpanzees remain unaffected since Jan. 1973
7. (E.U.) (Case III-18 in fig. 1, and cousin of Case 6 above)	UK	F 61	60.5	1. Ataxia 2. Dysarthria 3. L. extensor plantar 4. Dementia 5. Dysphasia 6. Absent reflexes in lower limbs with bilat. extensor plantar responses	Spongiform encephalopathy Amyloid angiopathy Loss of white matter in cerebral hemisphere Neurofibrillary tangles and granulovacuoler change in hippocampus	Cerebral cortex Cerebellum	On test, July 1977

Group 1. Cases Resembling the Gerstmann-Sträussler Syndrome

A total of 17 cases of GSS are used in this analysis: 10 cases published in the literature (Table 1) and 7 cases referred to our laboratory for virus isolation studies (Table 2). The cases come from seven different countries. Ten of the 17 cases occurred within 8 families with 60 other affected members.

Ages at death and durations of disease. The mean age at death of all 17 cases was 48 years (range 29 to 62 years) and the mean duration of disease was 59 months (range 13 to 132 months). There were 11 cases with possible or confirmed spongiform encephalopathy (*see* Tables 1, 2). The mean age at death of the 17 GSS cases (48.0 years, 10.7 years SD) was significantly less ($P = 0.001$) than that of the 97 cases of transmissible CJD without amyloid plaques (58.6 years, 9.4 years SD). The mean duration of illness of the 17 GSS cases (59.5 months, 33.7 months SD) was significantly ($P = 0.001$) longer than that of cases of transmissible CJD without amyloid plaques (6.2 months, 5.0 months SD). Similar relationships held if only the 11 cases of the GSS with spongiform change were compared with transmissible CJD without amyloid plaques.

The chief clinical features of the disease (Tables 1 and 2) are cerebellar signs, dementia, and pyramidal signs. The slow evolution of the illness is the main point of differentiation from the typical case of transmissible CJD. Myoclonus is not a constant finding. One unusual feature is the loss of reflexes in the lower limbs with preservation of extensor plantar responses, occurring in seven cases in the later stages of the illness. The peculiar crossed-arm reflex described originally by Gerstmann (1928) was not recorded in any other case, possibly because its presence was not sought.

The pathological changes in the previously published cases are summarized in the introductory historical review (Table 1). In this section we address three aspects based on the published cases and the cases referred to our laboratory: first, the clinical and pathological heterogeneity of the syndrome, including the presence or absence of spongiform change, and the variability of clinical and pathological features seen within a given family; secondly, the significance of white matter changes; finally, the varied morphology of the amyloid plaques. Each aspect will be related to the transmissibility of the disease determined by our experimental results (Tables 1 and 2).

The 'JW' family and the clinical and pathological heterogeneity of the GSS. The clinical and pathological heterogeneity of the GSS is well illustrated by reference to the family of J.W. (Cases 6 and 7 in Table 2; Mishra, 1974; Rosenthal *et al.*, 1976; and Adams, Scaravilli and Spokes, 1979). The genealogy of this family is presented in fig. 1, where 18 affected members occurred in 4 generations, consistent with an autosomal dominant mode of transmission. Little information is available on the affected identical twins in the first generation. The mean duration of illness, determined in 13 affected members, was 51 months (range 13 to 122 months). Seven of 17 affected members had a neurological disease with dementia (Cases II-4, III-5, 9, 12, 14, 18 and IV-2). Nearly all affected members had prominent cerebellar signs. Spinal cord and posterior column involvement was recorded in 8 members (Cases III-1, 2, 4, 7, 9, 12, 18 and IV-1). Paræsthesiæ were prominent symptoms in 6 members (Cases II-3, 6, III-2, 4, 7 and IV-1). Electromyographic evidence of lower motor neuron involvement was obtained in 2 cases (Cases III-7, 9).

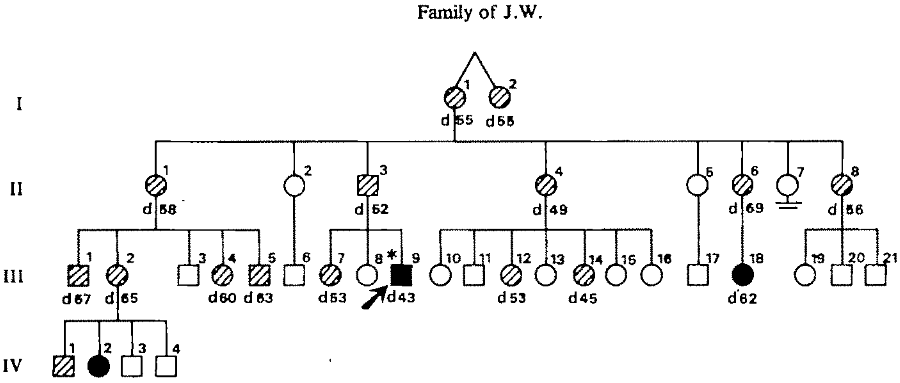

FIG. 1. The genealogy of the J.W. family. The propositus is indicated by an arrow. Ages at death where known are shown. The solid squares or circles are the three cases with pathologically confirmed spongiform change. Cross-hatching indicates other affected members.

Neuropathological examinations were secured in 5 cases (Cases III-5, 9, 12, 18 and IV-2). All showed a similar type of amyloid plaque deposition throughout the brain, typical of the GSS. Congophilic angiopathy was noted in one case (Case III-18). Three of the 5 cases had typical spongiform encephalopathic changes (Cases III-9, 18 and IV-2); a pathognomonic spongiform change was not present in the brains of the other two pathologically examined cases (Cases III-5, 12). The propositus (Case III-9 in fig. 1 and Case 6 in Table 2), with spongiform encephalopathy, had the shortest duration of illness (13 months) of all affected members. The clinical evolution of his disease was quite typical for CJD, with characteristic EEG changes recorded. Suspensions of brain from this patient were inoculated intracerebrally into spider and squirrel monkeys and chimpanzees. The spider and squirrel monkeys developed typical experimental spongiform encephalopathies after incubation periods of 20 to 30 months. The chimpanzees, however, remain unaffected after more than seven years, and would thus appear resistant to this strain of virus. The cousin of the propositus (Case III-18 in fig. 1 and Case 7 in Table 2), also with histologically confirmed spongiform encephalopathy, was originally diagnosed as Huntington's disease. Her duration of illness (60.5 months) was close to the mean duration seen in all affected members. Specimens of her brain were inoculated into a chimpanzee, spider monkey and guinea pigs more than three years ago. None have yet developed spongiform encephalopathies. Brain tissue from the two other cases (III-5, 12) without spongiform change are not available for transmission studies, and brain tissue from the most recent case (IV-2) with spongiform change was inoculated only recently into primates.

Important conclusions may be drawn from the study of this family. First, the occurrence of spongiform change in affected members is irregular and unpredictable, and does not correlate with clinical presentation (compare the subacute illness of Case III-9 with chronic illness of Case III-18). Secondly, the wide variety of clinical signs in this family, especially the presence or absence of dementia, myoclonus, and spinal cord involvement, emphasizes the inherent difficulty in the classification of sporadic cases that might fall within the spectrum of the GSS. Finally, the isolation of a virus causing a spongiform encephalopathy from Case III-9 in spider and squirrel monkeys but not in chimpanzees, and the apparent failure of transmission from the brain of Case III-18, may be a reflection on the strain variability of the CJD virus (Gibbs, Gajdusek and Amyx, 1979), and stresses the limitations of this bio-assay system in nonhuman primates which is at present the only method available for determining the transmissibility of this class of disease.

The presence or absence of spongiform change in relation to Transmissibility. When the pathological findings of all 17 cases summarized in Tables 1 and 2 are reviewed, it is seen that definite or possible spongiform change occurred in 11 cases. Of the 7 cases from which brain tissue was available for inoculation into nonhuman primates, a virus causing an experimental spongiform encephalopathy was isolated in 3 cases (Cases 1, 2 and 7 in Table 2), all 3 cases having spongiform change. Case 4, without spongiform change, although on test more than three years, cannot yet be considered a negative transmission since the source of inoculum was formalin fixed brain. Therefore no conclusions can yet be drawn on the presence or absence of a virus in the 3 specimen cases without spongiform changes (Cases 3, 4 and 5 in Table 2). It will be several years or more before any transmissions in this group can be expected.

White matter lesions in the GSS. White matter loss or degeneration revealed by routine and myelin stains was seen in variable degrees in 13 of the 17 GSS cases (Cases 1, 2, 3, 4, 5, 7, 8, 9 in Table 1; Cases 1, 2, 4, 5, 7 in Table 2). Most frequently affected areas were the corticospinal tracts and cerebral hemispheres (7 cases), spinocerebellar tracts (6 cases), cerebellum (5 cases), posterior columns, superior cerebellar peduncles, and brain-stem (2 cases). In most instances, it is not possible to determine to what degree this loss of myelin was secondary to neuronal loss. In the more typical case of CJD without amyloid plaques, white matter loss, especially in the corticospinal tracts, is usually in proportion to the degree of neuronal loss in the cerebral cortex (Masters and Richardson, 1978), which in turn is usually a reflection of the duration of illness. As noted above, the mean duration of illness of the GSS cases is considerably longer (by a factor of 10) than the mean duration of illness in cases of CJD without amyloid plaques.

On this basis alone it could be argued that any white matter loss would be of a secondary nature. However, in at least 2 cases in the present series (Cases 1 and 2 in Table 2), the degree of white matter loss was clearly in excess of the degree of neuronal loss in either the cerebral cortex and cerebellum. Moreover, when brain tissue from Case 1 was inoculated into mice, it induced a spongiform encephalopathy of the grey matter and at the same time a reproducible vacuolation and degeneration of the white matter in the cerebral cortex, cerebellum and brain-stem (Tateishi, Koga *et al.*, 1979; Tateishi, Sato, Koga, Doi and Ohta, 1980; Sato, Ohta and Tateishi, 1980; and unpublished data from our laboratory). However, transmission of the virus from Cases 1 and 2 into nonhuman primates in our laboratory caused only a typical spongiform encephalopathy of the grey matter without any white matter involvement.

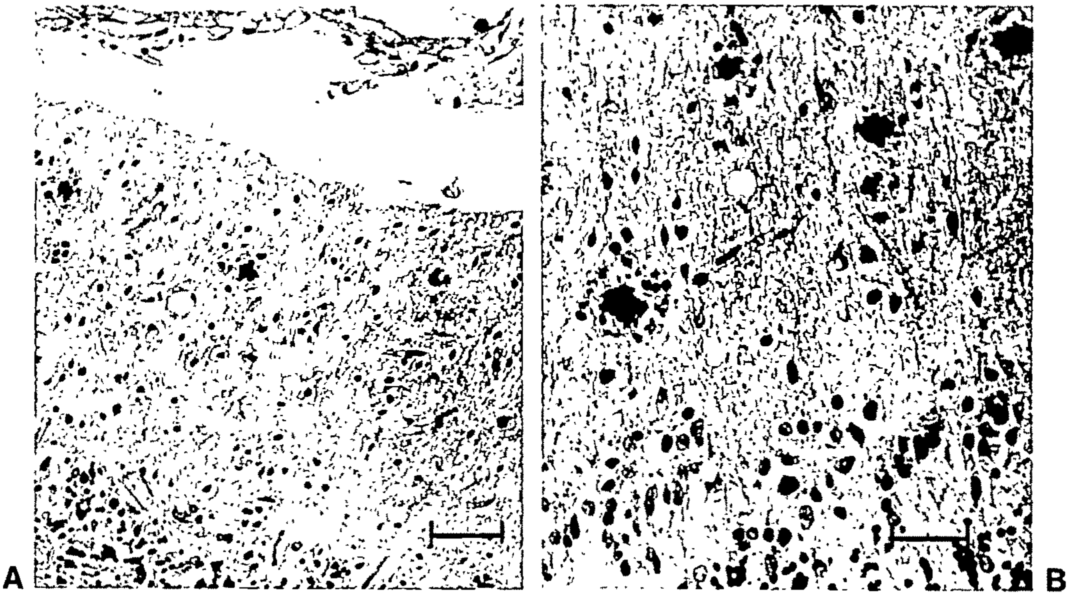

FIG. 2. Amyloid plaques of the GSS. Low and medium magnifications of the plaques in the molecular layer of Case 1, Table 2. There is also a spongiform change present in the molecular layer, with loss of granule cells and Purkinje cells, and an increase in the number of Bergmann glia. Scale bars = 60 μm (A), 40 μm (B). Periodic acid Schiff.

The morphology of amyloid plaques in the GSS. The differing morphologies of the amyloid plaques seen in selected cases referred to our laboratory are shown in figs. 2 to 4. In their most characteristic form, there is a central dense core of amyloid surrounded by smaller globules of amyloid (figs. 2, 3A, B, 4B, C). Many have an indistinct border as they merge into the neuropil (figs. 2C, D, 4A). Some assume shapes similar to the KP, with a delicate fibrillar pattern radiating from the central

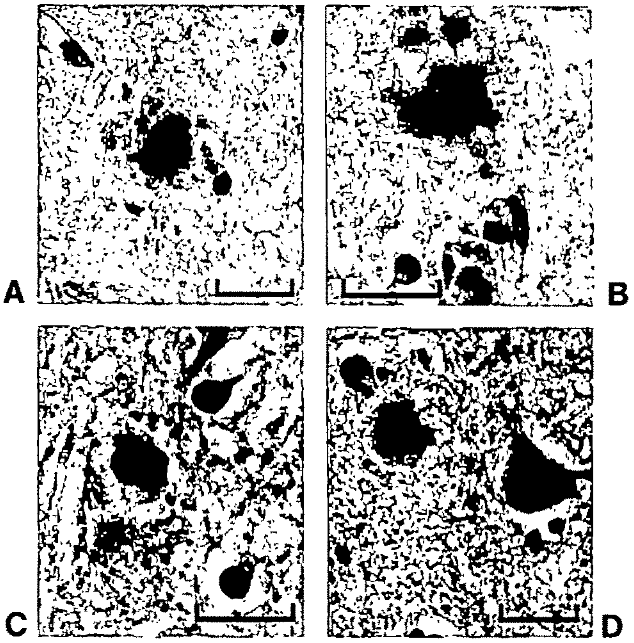

FIG. 3. Amyloid plaques of the GSS. A, B, higher magnifications of the amyloid deposits in the cerebellum of Case 1, Table 2. Smaller globules of amyloid are seen surrounding the central mass of the plaque. C, amyloid plaque from the cerebral cortex of Case 3, Table 2. The edge of the plaque merges indistinctly with the surrounding neuropil. D, Case 4, Table 2, illustrating an amyloid plaque with a radiating pattern similar to a KP. Scale bars = 25 μm (A, D), 20 μm (B, C). Periodic acid Schiff (A, B), hæmatoxylin and eosin (C, D).

amyloid core (figs. 3D, 4A). However, forms resembling the SP with surrounding glial and microglial reaction and neuritic degeneration are rarely seen. Ultrastructurally, the GSS amyloid plaque is seen to consist of a radiating fibrillar network of amyloid fibrils, with minimal if any neuritic degeneration (Motomura *et al.*, 1977; Hirano *et al.*, 1977; Schlote *et al.*, 1980), indistinguishable from the ultrastructure of the KP (*see below*). The distribution of these plaques is widespread throughout the brain (Table 2), most frequently in the cerebral cortex and cerebellum. Amyloid deposits of any kind have not been observed in any of the experimental primates infected with the virus isolated from any of these cases.

Group 2. Spongiform Encephalopathy with Kuru Plaques

Details of the 23 cases of CJD with KP are summarized in Table 3. The cases come from 10 different countries. With the exception of Case 2 of Zarranz, Rivera Pomar and Salisachs (1979), a possible familial case, all others are sporadic cases of CJD.

Ages at death and durations of disease. The mean age at death of cases of CJD with KP is 58.0 years (10.5 years SD) which is the same as the mean age of death of 97 cases of transmissible CJD without amyloid plaques (58.6 years, 9.4 years SD).

TABLE 3. PATIENTS WITH CREUTZFELDT-JAKOB DISEASE AND KURU PLAQUES

Identification and references	*Country of origin*	*Sex age (yrs)*	*Duration (months)*	*Chief symptoms and signs in order of appearance*	*Pathological findings in brain*	*Location of kuru plaques*	*Experimental data*
A. Cases reported to laboratory							
1. (Az.) Wolpow and Kleinman, 1980	Brazil	M 44	16	1. Vertigo 2. Ataxia 3. Dementia 4. Myoclonus	Spongiform encephalopathy	Cerebellum	Virus isolated in squirrel monkey
2. (Ba.)	USA	M 40	16	1. Ataxia 2. Nystagmus 3. Spasticity 4. Dementia with myoclonus	Spongiform encephalopathy	Cerebellum	Virus isolated in squirrel monkeys
3. (Bi.)	USA	F 71	32	1. Memory loss 2. Dementia 3. Spasticity in brain-stem 4. Myoclonus	Spongiform encephalopathy Lesions of Wernicke's encephalopathy Congophilic angiopathy	Frontal lobe	No specimens suitable for inoculation
4. (Cu.)	USA	M 72	5	1. Visual disturbances 2. Dementia 3. Dysmetria 4. Myoclonus	Spongiform encephalopathy Rare senile plaque in hippocampus	Occipital lobe	Virus isolated in squirrel monkeys
5. (D'An.)	USA	M 49	12	1. Tremor 2. Ataxia 3. Dementia 4. Myoclonus	Spongiform encephalopathy	Cerebellum	Squirrel monkey died without disease 48 m after inoculation with formalin-fixed brain
6. (D-H.) Hayek and Ulrich, 1975	Switzerland	F 70	12	1. Ataxia 2. Vertigo 3 Dementia	Spongiform encephalopathy	Cerebellum	On test, formalin-fixed brain inoculated May 1977
7. (Do.)	USA	M 65	5	1 Ataxia 2 Dizziness 3. Confusion 4. Death 2 m after craniotomy for aneurysm	Spongiform encephalopathy Intracerebral hæmorrhage and anoxic changes consistent with post-operative course	Cerebellum	On test, formalin-fixed brain inoculated July 1977; frozen brain inoculated Feb., 1979
8. (Fe.)	USA	F 67	10	1. Dementia 2. Ataxia 3. Myoclonus	Spongiform encephalopathy	Occipital lobe	No specimens suitable for inoculation
9. (He.) Case 1 of Zarranz *et al.*, 1979	Spain	M 62	10	1. Ataxia 2. Dementia 3. Startle reaction	Spongiform encephalopathy	Cerebellum Putamen Thalamus	Not yet inoculated
10. (Ka.)	USA	M 70	15	1. Ataxia 2. Dementia	Spongiform encephalopathy	Cerebellum	On test, formalin-fixed brain inoculated April 1979
11. (La.)	USA	M 72	3	1. Dysarthria 2. Ataxia 3. Dementia	Spongiform encephalopathy	Cerebellum	On test, April 1979
12. (Ma.) Gajdusek *et al.*, 1974; Schoene *et al.*, 1981	USA	M 54	18	1. Paresthesia 2. Vasculitis 3. Ataxia 4. Nystagmus 5. Vertigo 6. Dementia 7. Myoclonus	Spongiform encephalopathy White matter vacuolation of brain-stem, spinal cord Healed vasculitis	Cerebral cortex	Virus isolated in 3 chimpanzees and 4 squirrel monkeys Virus titre in brain 10^{-4} in fectious units per g. Virus isolated from lung and pooled spleen and kidney
13. (Si.) Chou and Martin, 1971	USA	M 64	12	1. Dementia 2 Visual hallucinations 3. Ataxia	Spongiform encephalopathy	Cerebellum	On test, formalin-fixed brain inoculated January 1980
14. (Sl.)	USA	F 60	16	1. Ataxia 2. Dysarthria 3. Dementia 4. Choreoathetosis	Spongiform encephalopathy	Cerebellum	Not yet inoculated

TABLE 3 (*continued*)

Identification and references	*Country of origin*	*Sex age (yrs)*	*Duration (months)*	*Chief symptoms and signs in order of appearance*	*Pathological findings in brain*	*Location of kuru plaques*	*Experimental data*
B. Cases Reported in the Literature							
15. Horoupian *et al.*, 1979	Jamaica	F 54	12	1. Ataxia 2. Dementia 3. Myoclonus	Spongiform encephalopathy	Cingulate gyrus Thalamus	—
16. Krücke *et al.*, 1973 (Case 1)	W. Germany	F 53	15	1. Dementia 2. Ataxia 3. Extrapyramidal tremor	Spongiform encephalopathy Occasional neurofibrillary tangle in cerebral cortex	Cerebellum Cerebral cortex (rare) Ammon's horn	—
17. Krücke *et al.*, 1973 (Case 2)	W. Germany	M 45	11	1. Difficulty walking 2. Dementia	Spongiform encephalopathy	Cerebellum	—
18. Krücke *et al.*, 1973 (Case 3)	W. Germany	F 43	7	1. Giddiness 2. Ataxia 3. Diplopia 4. Amnestic syndrome	Spongiform encephalopathy	Cerebellum	—
19. Adams *et al.*, 1974	UK	F 47	16	1. Ataxia 2. Dementia	Spongiform encephalopathy	Cerebellum	—
20. Indravasu, 1975	Thailand	M 48	12	1. Headache 2. Dementia 3. Ataxia	Spongiform encephalopathy	Cerebral grey and white matter Cerebellar white matter	—
21. Toro-Gonzalez, 1978	Columbia	M 60	48	No information	Spongiform encephalopathy	Cerebellum	—
22. Brucher *et al.*, 1979	Belgium	F 56	19	1. Dementia 2. Cerebellar signs 3. Myoclonus	Spongiform encephalopathy	Cerebellum	—
23. Zarranz *et al.*, 1979 (Case 2)	Spain	F 69	17	1. Ataxia 2. Dementia 3. Myoclonus (Possible familial case)	Spongiform encephalopathy	Cerebellum Cerebral cortex Putamen Thalamus	—

However, the mean duration of disease of CJD with KP is 14.7 months (9.4 months SD) which is significantly ($P < 0.001$) longer than the mean duration of disease in the 97 transmitted cases of CJD without amyloid plaques (6.2 months, 5.0 months SD).

The majority of cases with KP (20 of 23) have early and persisting cerebellar signs or symptoms, which correlates well with the distribution of KP in the cerebellum (Table 3). However, 3 of the 4 cases with KP only in the cerebral cortex also had some cerebellar symptoms and signs, although not prominent. Only one case had rare senile plaques in the hippocampus, and one other had occasional neurofibrillary tangles in the cerebral cortex. Virus inducing a spongiform encephalopathy in experimentally inoculated nonhuman primates was isolated from 4 of the 14 cases referred to our laboratory; brain tissue from 5 other cases is still on test for the presence of virus. Amyloid plaques have not been seen in the brains of experimentally infected primates, irrespective of whether the inoculum was from a brain with amyloid plaques or not.

A representative KP is illustrated in fig. 5A. Here, the typical round homogeneous central core surrounded by a radiating pattern of fibrils is seen. The ultrastructural features of KP in CJD have been described by others (Chou and Martin, 1971; Horoupian, Powers and Schaumburg, 1972; Krücke, Beck and Vitzthum, 1973;

Brucher, de Castro Costa and Laterre, 1979) and are seen to consist of filaments of diameter 7 to 13 nm, without evidence of surrounding degenerative neuritic processes. The amyloid nature of these plaques has been consistently confirmed by their binding of congo red with resulting anisotropism in polarized light.

One of the four cases from which virus was isolated (Case 12, Table 3) presented with paræsthesia and brain-stem signs, and also had a vacuolation of the white matter of the spinal cord and brain-stem. On these criteria alone, a resemblance with the GSS is seen, and this case would have been classified as such were it not for the occurrence of KP as distinct from the amyloid plaques more characteristic of the GSS. This case (described in detail elsewhere by Schoene, Masters, Gibbs, Gajdusek, Tyler and Dammin, 1981) illustrates the difficulty in classification based on the morphology of the amyloid plaque alone, and further suggests the continuous spectrum which exists between CJD with KP and the transmissible cases of the GSS.

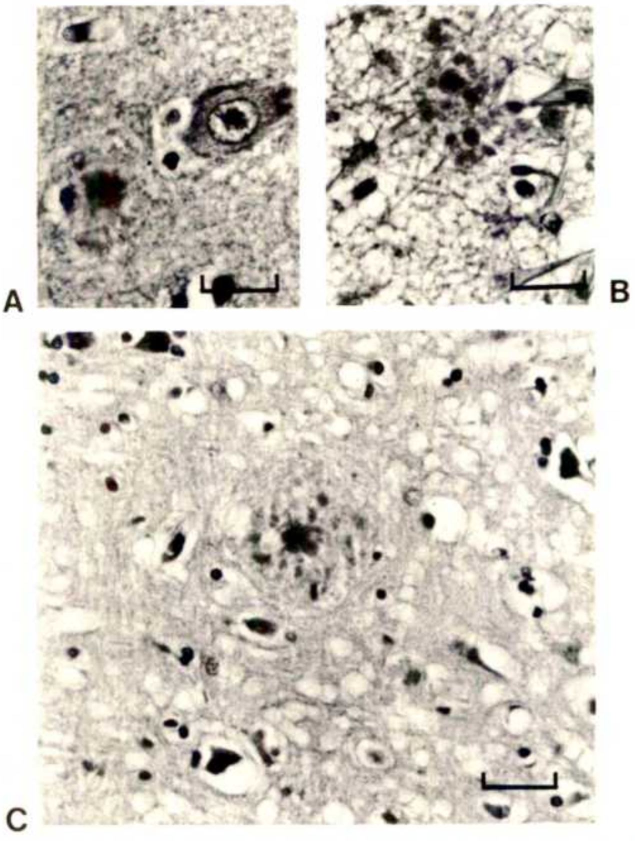

FIG. 4. Amyloid plaques in the GSS. A, B, plaques seen in the cerebral cortex of Case 5, Table 2. In the deeper layers of the cortex, the amyloid merges indistinctly with the neuropil (A), and in the more superficial molecular layer, globular deposits are seen (B). C, amyloid plaque in Case 6, Table 2, also showing the severe degree of spongiform change. Scale bars = 25 μm (A, B), 40 μm (C). Hæmatoxylin and eosin.

Human kuru, with and without kuru plaques. For comparison with this group of CJD with KP, cases of human kuru with and without KP were reviewed. Twenty-eight of 38 cases of human kuru (74 per cent) had KP in a distribution similar to those found in CJD (Table 3). In human kuru with and without KP, a comparison between ages at death is not valid because of the skewed age distribution of kuru patients towards children and adolescents (Gajdusek, 1977; Alpers, 1979). However, the mean duration of disease of 26 cases with KP was 11.0 months (3.2 months SD), which is significantly ($P < 0.001$) longer than the mean duration of disease in 10 cases without KP (6.1 months, 1.8 months SD). By definition, the KP in human kuru does not differ morphologically from the KP seen in CJD, and ultrastructurally, the KP of human kuru is also composed of amyloid filaments 7 to 10 nm in diameter (Field *et al.*, 1969; Zu Rhein, 1969).

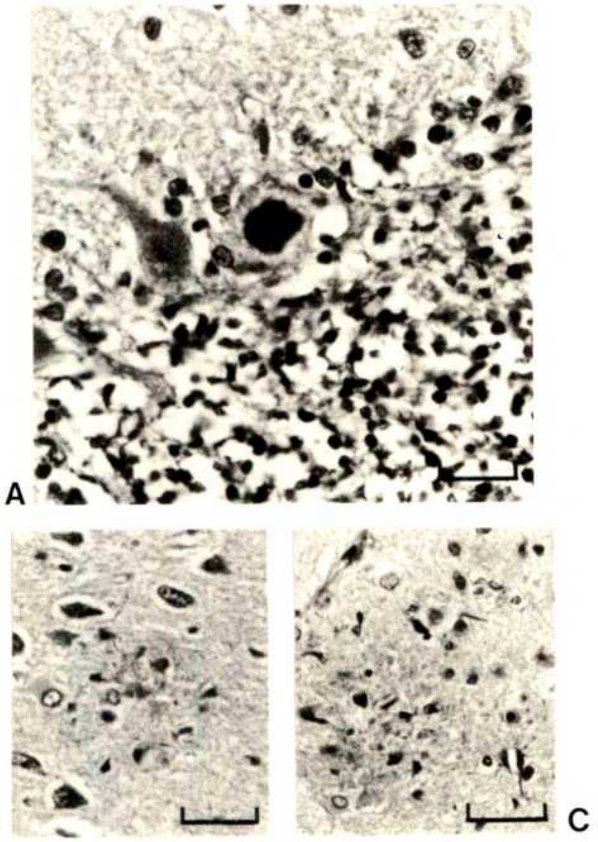

FIG. 5. Kuru plaque and neuritic senile plaques. A, typical kuru plaque seen at the junction of the molecular and granule cell layers of the cerebellum of Case 10, Table 3. The solid dense central core of amyloid is surrounded by a halo of fine radiating fibrils. B, C, typical neuritic senile plaques seen in the hippocampus of a case with Alzheimer's disease. There is very little amyloid in the centre of the plaques, which are surrounded by astrocytes and microglia. Scale bars = 25 μm (A), 40 μm (B, C). Hæmatoxylin and eosin.

Group 3. Spongiform Encephalopathy with Senile Plaques

We ascertained a total of 22 cases of clinically typical CJD with mixtures of amyloid and neuritic senile plaques (SP). Details of these cases are summarized in Table 4. The cases come from seven different countries, and all are sporadic with the exception of Case 14 (Table 4) which is a possible familial case.

Ages at death and durations of disease. The mean age at death of the 22 cases of CJD with SP is 64.4 years (5.9 years SD), which is significantly ($P = 0.001$) greater than the 58.6 years found in 97 cases of transmissible CJD without amyloid plaques. The mean duration of disease of CJD with SP (11.1 months, 11.8 months SD) is not significantly different from the mean duration of disease of the 97 cases of transmissible CJD without amyloid plaques (6.2 months, 5.0 months SD).

Only 5 of the 22 cases with SP had prominent cerebellar signs or symptoms, and in only one case were SP found in the cerebellum (but without signs of cerebellar involvement). Virus causing an experimental spongiform encephalopathy was isolated from the brain of 6 of the 12 cases in which suitable tissue was available for inoculation (Table 4). Of the remaining 6 specimen cases, only one (Case 13) has been on test more than four years, and can be considered a failed transmission.

The question arises whether the occurrence of SP in these cases is more than would be expected in a similar number of age-matched controls without neurological disease, or represents the concurrence of two diseases, CJD and AD. The mean age at death of this group of cases, compared to the more typical cases of CJD, would certainly suggest that an age-related bias is involved. Half of the cases had neurofibrillary tangles, some in areas remote from the hippocampus. In none of the cases has it been possible to quantitate the numbers of SP. However, in at least 8 of these cases (Cases 4, 5, 6, 8, 10, 12, 17 and 20 in Table 4), a qualitative assessment based on the routine evaluation of representative areas of brain suggests that the number of SP present in areas of cerebral cortex remote from the hippocampus is far greater than would be expected in non-demented age-matched controls, and is consistent with the number of plaques usually identified in otherwise typical cases of AD. Moreover, the number of SP in these cases seems to be out of proportion to the degree of neurofibrillary change. In our series, there have been no cases of CJD with neurofibrillary changes in the absence of amyloid plaque deposition.

Representative illustrations of neuritic senile plaques of AD are presented in figs. 5B, C. Here they are seen as quite distinctive entities from the plaques in the GSS and KP.

DISCUSSION

The Gerstmann-Sträussler syndrome may be defined as a chronic cerebellar ataxia, with the deposition of amyloid plaques which assume shapes intermediate between the KP and the amyloid SP. Dementia, spinal cord or tract involvement, and spongiform change occur frequently but not invariably. As with other

TABLE 4. PATIENTS WITH CREUTZFELDT-JAKOB DISEASE AND SENILE PLAQUES

Identification and references	*Country of origin*	*Sex age (yrs)*	*Duration (months)*	*Chief symptoms and signs in order of appearance*	*Pathological findings in brain*	*Location of senile plaques*	*Experimental data*
A. Cases reported to laboratory							
1. (Au.)	France	F 62	19	1 Headache 2. Dementia 3. Myoclonus	Spongiform encephalopathy	Cerebellum	On test, January 1980
2. (Ba.)	France	M 64	11	1. Dementia 2. Difficulty walking 3. Dysarthria 4. Myoclonus	Spongiform encephalopathy (biopsy only)	Cerebral cortex (biopsy only)	On test, Feb. 1979
3. (Ca.)	USA	M 53	31	1. Dementia 2. Rigidity 3. Myoclonus	Spongiform encephalopathy	Cerebral cortex	Virus isolated in squirrel monkeys
4. (En.)	Canada	M 64	45	1. Dementia 2. Myoclonus 3. Rigidity	Spongiform encephalopathy Lewy bodies in substantia nigra	Cerebral cortex Hippocampus	On test, May 1977
5. (Gr.) Horoupian and Ross, 1975	Canada	F 66	9.5	1. Ataxia 2. Dementia	Spongiform encephalopathy	Cerebral cortex	On test, April 1979
6. (Ha.)	USA	F 60	3	1 Dementia 2. Startle response 3. Hypertonia	Spongiform encephalopathy Some neurofibrillary tangles	Cerebral cortex	Virus isolated in guinea pigs
7. (Le.)	USA	M 64	4	1. Visual disturbance 2. Dementia	Spongiform encephalopathy (biopsy only)	Cerebral cortex (biopsy only)	On test, Nov. 1977
8. (Ma.) Hirano *et al.*, 1972 (Case 1)	USA	F 69	8	1. Ataxia 2. Dementia 3. Myoclonus	Spongiform encephalopathy Some neurofibrillary tangles	Cerebral cortex Hippocampus, Caudate, putamen	Virus isolated in squirrel and spider monkeys
9. (C.Mo.)	UK	F 68	11	1. Dementia 2. Seizures 3. Myoclonus 4 Rigidity	Spongiform encephalopathy Amyloid angiopathy (biopsy only)	Cerebral cortex	Virus isolated in squirrel monkey
10. (D.Mo.)	USA	M 56	4.5	1. Ataxia 2. Dementia	Spongiform encephalopathy Neurofibrillary change in hippocampus	Cerebral cortex	Virus isolated in squirrel and capuchin monkeys
11. (Mu.)	USA	F 55	15	1. Dementia 2. Hemianopsia 3. Rigidity 4. Myoclonus	Spongiform encephalopathy Neurofibrillary change in hippocampus	Hippocampus	Virus isolated in a chimpanzee and spider monkey
12 (Na.)	USA	F 78	3.5	1. Dementia 2. Cortical blindness 3. Myoclonus	Spongiform encephalopathy	Cerebral cortex	No specimens suitable for inoculation
13. (Pe.)	USA	M 59	36	1. Dementia 2. Extra-pyramidal signs	Spongiform encephalopathy (biopsy only)	Cerebral cortex (biopsy only)	On test, April 1974
B. Cases reported in literature							
14. Shiraki and Matsuoka, 1963 (Case 2)	Japan	M 70	7	1. Memory loss, withdrawal 2. Disorientation 3. Hand tremor	Spongiform encephalopathy Neurofibrillary tangles in hippocampus	Hippocampus	—
15. Amyot and Gauthier, 1964 (Case 1)	France	F 64	3	1. Visual disturbance 2. Myoclonus 3. Dementia	Spongiform encephalopathy Some neurofibrillary tangles in cerebral cortex	Cerebral cortex	—
16. Colle and Miranda-Nives, 1967	Belgium	M 63	13	1. Dementia 2. Hypertonia 3. Hyperreflexia	Spongiform encephalopathy Some neurofibrillary tangles in hippocampus	Hippocampus Temporal cortex	—
17. Kirschbaum, 1968 (Case XIV)	USA	F 64	5	1. Ataxia 2. Dementia 3. Myoclonus	Spongiform encephalopathy Some neurofibrillary tangles in hippocampus	Cerebral cortex Hippocampus	—
18. Ishida *et al.*, 1971	Japan	M 63	4	1. Dementia 2. Visual failure 3. Rigidity 4. Myoclonus	Spongiform encephalopathy Occasional neurofibrillary tangles in cerebral cortex	Cerebral cortex	—
19. Hamaguchi *et al.*, 1972	Japan	F 64	2	1. Dementia 2. Myoclonus 3. Rigidity	Spongiform encephalopathy	Frontal cortex	—
20. Hirano *et al.*, 1972 (Case 2)	USA	F 67	3	1. Visual disturbance 2. Dementia	Spongiform encephalopathy Some neurofibrillary tangles in hippocampus	Cerebral cortex Basal ganglia	—
21. Hogenhuis *et al.*, 1977	The Netherlands	F 76	4	1. Dementia 2 Myoclonus	Spongiform encephalopathy Congophilic angiopathy	Cerebral cortex	—
22. Gaches *et al.*, 1977	France	M 68	2.5	1. Dementia 2. Hypertonia 3. Myoclonus	Spongiform encephalopathy Neurofibrillary tangles in subiculum Occasional amyloid change in superficial cortical vessels	Cerebral cortex Hippocampus Amygala	—

spinocerebellar ataxias (Greenfield, 1954), clinical and pathological heterogeneity even within an affected family are seen. We conclude that at least some cases within this syndrome represent variants of a CJD type virus-induced spongiform encephalopathy. This conclusion is based on the isolation of a virus causing an experimental spongiform encephalopathy from the brains of 3 cases: 2 cases in which the clinical evolution of disease was consistent with the GSS, and one case in which the clinical evolution of disease was more typical of CJD, but where the family history was more consistent with the GSS. The most striking clinical feature of the syndrome is the slow evolution and long duration of disease when compared to the typical case of transmissible CJD. Although the GSS was originally described as a familial disease, sporadic cases conistent with this syndrome occur, and therefore present a problem analogous to the familial and sporadic occurrence of CJD (Masters, Gajdusek, and Gibbs, 1981). In the 17 cases of the GSS reviewed in Tables 1 and 2, and in the J.W. family, the clinical and pathological variability of the syndrome is seen, and for this reason it would seem unwise to place a rigid definition on the syndrome until such time as more cases can be studied for the presence or absence of a causative virus of the CJD type.

Pathologically, three aspects of the syndrome require discussion: the presence or absence of spongiform change; the nature of the amyloid deposition; and the significance of white matter degeneration.

Spongiform change in the grey matter was recorded in 11 of the 17 cases of the GSS. In many of the cases recorded only in the literature, it is not possible to be sure that the vacuolation described is characteristic of CJD, or represents some other form of status spongiosus (Masters and Richardson, 1978). All 3 cases where a virus was isolated did have typical spongiform vacuolation of the neuropil, but further studies are required before it can be determined whether those cases without spongiform change are transmissible. Experiments are now in progress to answer this question. The variability of spongiform change in natural and experimental scrapie suggest that the absence of this change in the human brain be interpreted cautiously (Marsh, Sipe, Morse and Hanson, 1976; Fraser, 1979; Hadlow, Kennedy, Race and Eklund, 1980).

The forms of amyloid plaques seen in cases of the GSS are intermediate between the amyloid KP of CJD, kuru, and scrapie, and the amyloid SP of AD. The main point of differentiation from SP at a light microscopic level is the relative lack of glial and microglial reaction and little or no neuritic degeneration surrounding KP and the plaques in the GSS. However, it is well-known that the SP of AD assume varied forms, ranging from the neuritic (primitive or classical) type with little amyloid in its centre to the amyloid type with little or no neuritic elements seen at the periphery (Wiśniewski and Terry, 1973). It is this latter type of amyloid SP that most closely resembles the KP and the plaques of the GSS. Ultrastructurally, the amyloid plaques of the GSS, the KP, and the amyloid SP have a very similar appearance. Similarly, the amyloid plaques that occur in natural and experimental scrapie more closely resemble the KP and the plaques of the GSS, but may have a neuritic and a glial reactive component, seen at an ultrastructural level (Bruce and Fraser, 1975).

While the nature of the amyloid constituting the plaque in any of these diseases is unknown, and the sequence in the formation of the SP is debated (Wiśniewski and Terry, 1973), the presence of a continuous spectrum of plaque morphology between patients suggests a common pathogenesis. One factor that may be involved in the varied morphology of these plaques could be the temporal sequence following the deposition of amyloid in the brain parenchyma. Examination of the mean durations of illness in the groups examined in the present study (summarized in Table 5) show that KP occur in cases of CJD and kuru that have a significantly longer duration of illness than cases without amyloid plaques. Cases of GSS, where the duration of illness is almost ten times that of CJD without amyloid plaques, have massive amyloid deposition that bridges the spectrum of morphology of the KP to the amyloid type of SP. AD itself, with the longest duration of illness, is characterized by a mixture of amyloid and neuritic plaques. There are no formal studies in AD concerning the relative incidence of amyloid SP compared to neuritic SP, but cases of AD of relatively short duration (six years or less) have proportionately more of the amyloid centred SP than the neuritic type of SP (C. L. Masters, unpublished data). It is also known that the amyloid plaques of experimental scrapie occur most frequently when the strain of virus and host genotype result in a long incubation period (Bruce *et al.*, 1976). These observations strongly suggest that the morphology of the plaque is determined to a large extent by the duration of illness, or some other time-related function, such that the initial deposition of amyloid in the brain

TABLE 5. COMPARISON OF AGES AT DEATH AND DURATIONS OF ILLNESS IN DISEASES ASSOCIATED WITH AMYLOID PLAQUE DEPOSITION

	No. of cases	*Mean age at death (yrs)*[1]	*Mean duration of illness (months)*[1]
Transmissible Creutzfeldt-Jakob disease without amyloid plaques	97	58.6	6.2
Creutzfeldt-Jakob disease with kuru plaques	23	58.0 NS	14.7 ***
The Gerstmann-Sträussler syndrome	17	48.0 ***	59.5 ***
Human kuru without kuru plaques	10	—[2]	6.1
Human kuru with kuru plaques	26	—[2]	11.0
Creutzfeldt-Jakob disease with senile plaques	22	64.4 ***	11.1 NS
Alzheimer's disease[3]	(estimate)	65–75	72–144

[1] Significance values calculated in comparison to values of transmissible CJD without amyloid plaques. NS = not significant; *** = $P \leqslant 0.001$. [2] Mean age at death of human kuru not computed because of the skewed age distribution towards children and adolescents. The mean duration of illness of kuru with KP is significantly longer ($P < 0.001$) than the mean duration of kuru without KP. [3] The values for Alzheimer's disease are estimates since reliable data are not available.

assumes a stellate pattern and subsequently a glial response, and neuritic degeneration occurs. The origin of the amyloid is at present unknown, but the favoured current hypotheses concern its vascular origin, as seen in the irregular association of amyloid plaques with a congophilic angiopathy, with at least one component of the plaque possibly of immunoglobulin origin (Mandybur, 1975; Ishii and Haga, 1976). It is of interest to note that in the original cases of the GSS, amyloid deposits were described within and attached to the endothelium of blood vessels.

The topographic dispersion of the amyloid plaques *per se* does not appear to be a major factor determining their morphology. While KP are most frequently seen in the cerebellum, they also occur less frequently in other areas of the brain. SP in both CJD and AD are seen most frequently in the hippocampus, adjacent temporal cortex, and elsewhere in the cerebral cortex. Infrequently, SP of AD are found in the cerebellum, where they tend to be mainly of the amyloid variety with a resemblance to KP (Pro, Smith and Sumi, 1980). In cases of AD of long duration (six years or more) amyloid-centred plaques are more prominent in areas of cerebral cortex remote from the fronto-temporal regions, where the brunt of the disease occurs (C. L. Masters, unpublished data). Rather than postulate that the regional substrate of the brain parenchyma determines this disparity in morphology, a more parsimonious explanation is provided by the hypothesis that the temporal sequence of amyloid deposition determines morphology, in that the stellate amyloid plaques of the cerebellum or elsewhere form at a later stage (that is, are more recent) than the SP with little amyloid and surrounding reactive changes. It is of some interest that typical KP occurring in the absence of SP have not been described in association with Alzheimer's neurofibrillary change, nor have SP ever been observed in cases of human kuru.

The occurrence of SP in CJD as recorded in this paper may only be coincidental, occurring in a significantly older age group of CJD patients compared to those without amyloid plaques (Table 5). Nevertheless, the spectrum of plaque morphology emphasized in this paper suggests that a common pathogenic factor is involved, even if plaque formation eventually turns out to be a secondary phenomenon unrelated to the presence of a virus. Other types of cerebrovacular amyloidosis with plaque deposition (reviewed by Shaw, 1979) share some clinical and pathological similarities to the GSS, and prompt an investigation of these cases to test for the presence of a transmissible virus.

Degenerative changes in the white matter are common, often prominent, features of the cases of GSS, particularly in the brain-stem, cerebellum and spinal cord. Undoubtedly, some of these can be attributed to secondary Wallerian degeneration consequent upon neuronal cell loss. In certain cases, this white matter involvement was out of proportion to the degree of neuronal loss. Our own and Tatieshi's observations on the white matter involvement in experimentally infected rodents (but not primates) in one particular isolate (Case 1, Table 2) demonstrate that the virus indeed might cause a destruction of white matter by mechanisms as yet undetermined. We have observed several other cases of CJD, without amyloid plaque deposition, in which the white matter was extensively involved (G. Kleinman and E. P. Richardson, personal communication; C. L. Masters, unpublished data). Furthermore, white matter vacuolation in experimental scrapie, as with amyloid plaques, has been observed to be related to the particular virus strain-host genotype combination (Fraser, 1976, 1979). For these reasons, it seems probable that certain strains of the virus, in an appropriate host, will affect the white matter, and provide more evidence that the GSS is a variant of CJD.

SUMMARY

Four patients with atypical Creutzfeldt-Jakob disease (CJD), whose brain tissue transmitted an experimental spongiform encephalopathy to nonhuman primates, showed clinical and pathological similarities with the Gerstmann-Sträussler syndrome (GSS), a chronic cerebellar ataxia with unusual amyloid plaque deposition in the brain. Two of these patients clinically and pathologically were consistent with the GSS, one patient had the typical clinical features of CJD but had a family history of the GSS, and one patient had some of the clinical and pathological features of the GSS but had amyloid kuru plaques (KP) in the brain.

A review of the various forms of amyloid plaque deposition in 34 cases of typical or atypical CJD referred to our laboratory showed that 7 cases could be classified as GSS, 14 cases had KP, and 13 cases had amyloid senile plaques (SP) of the Alzheimer type. The forms of amyloid plaque deposited in the GSS are intermediate between the KP and the amyloid SP. Pooling the data from these 34 cases with a further 28 cases reported in the literature, the calculated mean duration of illness of CJD with KP (14.7 months) is significantly longer than the mean duration of illness of typical CJD without amyloid plaques (6.2 months). The mean duration of illness of patients with the GSS (59.5 months) is intermediate between CJD and Alzheimer's disease (AD). SP occurred in patients with CJD in an age group significantly older than CJD without amyloid plaques.

We conclude that at least some cases of the GSS are variants of transmissible CJD, and that the amyloid plaques of the GSS, the KP of the spongiform encephalopathies, and the SP of AD may share a common pathogenesis, their differing morphologies determined in part by temporal factors related to the duration of illness. Based on data derived from the occurrence of amyloid plaques in natural and experimental scrapie, the strain of virus and the genotype of the host must also be taken into account.

The demonstration that a group of chronic cerebellar ataxias with amyloid plaques are transmissible, and related to CJD, considerably broadens the spectrum of the transmissible virus dementias. This group most closely resembles the syndrome originally described by Gerstmann and Sträussler, provides a continuing impetus for the search for a virus ætiology of other forms of sporadic and familial cerebellar ataxias, and may provide insight into the pathogenesis of the SP of AD.

ACKNOWLEDGEMENTS

We thank the physicians who referred material to our laboratory for transmission studies, particularly Drs J. W. Boellaard, L. W. Duchen and J. Tateishi who also commented on the manuscript.

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(*Received September 16, 1980*)

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FRIEDREICH'S ATAXIA: A CLINICAL AND GENETIC STUDY OF 90 FAMILIES WITH AN ANALYSIS OF EARLY DIAGNOSTIC CRITERIA AND INTRAFAMILIAL CLUSTERING OF CLINICAL FEATURES

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INTRODUCTION

NICHOLAUS Friedreich was Professor of Medicine in Heidelberg when he described a distinctive clinical syndrome in 9 members of 3 sibships. He reported his findings in a series of five papers between 1863 and 1877 (Friedreich 1863*a*, *b*, *c*, 1876, 1877). The age of onset was around puberty. Ataxia and dysarthria were prominent; sensory loss and muscle weakness were late findings. Nystagmus was an inconsistent feature. Friedreich did not comment on the loss of tendon reflexes in his cases until his later papers as these reflexes were not described until 1875 (Erb, 1875). He noted the presence of scoliosis, foot deformity and cardiac symptoms in his patients.

Despite an initial reluctance to accept this disease entity by Charcot, the term of Friedreich's ataxia was proposed by Brousse in 1882 and Ladame was able to review a total of 165 reported cases in 1890. Ladame (1890) observed that the diagnosis was doubtful in many of these and that there was a tendency for the label of Friedreich's ataxia to be applied somewhat indiscriminately; some of the cases were 'incomplete, doubtful or even absolutely foreign to Friedreich's disease'. This tendency has continued and has led to confusion in the literature concerning 'transitional' and 'abortive' forms of the disease. The main source of this confusion is in relation to the distinction of cases of Friedreich's ataxia (FA) from some of those with Charcot-Marie-Tooth disease or hereditary motor and sensory neuropathy (HMSN). This disorder was first adequately documented shortly after FA (Charcot and Marie, 1886; Tooth, 1886). In 1911 Greenfield described a man said to have signs of FA and peroneal muscular atrophy. The report describes typical features of FA (with dysarthria, ataxia, areflexia and nystagmus). The patient did have distal wasting, but this does not exclude a diagnosis of FA. The major controversy concerning this issue did not arise until Roussy and Lévy (1926) described a family containing seven individuals affected with a disorder characterized by areflexia, difficulty in walking, distal weakness and occasional wasting, 'awkward hand movements', occasional tremor and pes cavus. The disease was dominantly inherited. None had sensory loss, definitely extensor plantar responses, dysarthria or nystagmus. Most of the patients had either congenital or acquired syphilis. The authors felt that the disorder they described was unique but that it resembled Charcot-Marie-Tooth disease most closely. They stated: 'We do not feel that this illness represents either an atypical form of Friedreich's ataxia or an intermediate form of other familial diseases. . . . these hypotheses complicate rather than elucidate, and raise the possibility of a unified pathogenesis for all the familial illnesses.' Symonds and Shaw (1926) reported two similar families almost simultaneously and suggested that the disease was a '*forme fruste*' of peroneal muscular atrophy. This was supported by the presence of an individual in one family with 'classical' Charcot-Marie-Tooth disease. Rombold and Riley (1926), however, considered nearly indentical patients to have 'an abortive form of Friedreich's disease'. The concept of the Roussy-Lévy syndrome being a variant of FA was later put forward by Darré, Mollaret and Landowski (1933), Dereux (1948) (who described relatives of the original Roussy-Lévy family), van Bogaert and Moreau (1939) and Wilson (1940). There were also reports of Charcot-Marie-Tooth disease, the Roussy-Lévy syndrome and FA all occurring in the same family (Beauchesne, 1936; Spillane, 1940; Roth, 1948; Shepherd, 1955). The cases of Beauchesne, Roth and Shepherd are, in retrospect, clearly all examples of HMSN. Spillane (1940) described a family in which Charcot-Marie-Tooth disease was dominantly inherited. In one sibship, an individual did have dysarthria and pyramidal signs in the lower limbs; she was markedly more disabled than her relatives. It appears that HMSN and FA did coexist within the same family in this instance. This is not that surprising, for neither disorder is particularly uncommon.

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There is now good evidence that the Roussy-Lévy syndrome is an expression of the gene for HMSN type I (or hypertrophic form). Tremor and/or ataxia is by no means rare in this disorder: it occurs in 39 per cent (Harding and Thomas, 1980*a*). The Roussy-Lévy syndrome occurs in patients with other family members demonstrating the typical clinical features of type I HMSN (Symonds and Shaw, 1926; Dyck and Lambert, 1968*a*; Harding and Thomas, 1980*a*). Furthermore, this syndrome is not sharply distinct clinically from HMSN type I, as there is a continuous spectrum of clinical features within this disorder with tremor and/or ataxia being absent, mild, moderate or marked, even within the same family. The neurophysiological and histological features of the Roussy-Lévy syndrome and type I HMSN are identical. Lapresle and Salisachs (1973) demonstrated hypertrophic changes with characteristic onion bulb formations in a nerve biopsy from one of Roussy and Lévy's original cases.

One important feature in distinguishing between Friedreich's ataxia and the 'Roussy-Lévy variant' of HMSN is that most of the latter are dominantly inherited. Nevertheless, recessive forms of HMSN type I have been reported and 2 out of 8 patients described by Harding and Thomas (1980*b*) had been incorrectly diagnosed as FA in the past. The prognosis in such cases is much better than in FA. In difficult early cases the distinction can easily be made on the basis of nerve conduction studies, but it appears that in the past much confusion has arisen from lack of acceptance of ataxia occurring in HMSN and amyotrophy in FA.

Another source of uncertainty in the definition of Friedreich's ataxia has been whether retained tendon reflexes are found in the disease. Ladame (1890) felt that the presence of knee or ankle jerks excluded the diagnosis. Wilson (1940), on the basis of his own cases, found this view untenable. Tyrer (1975) stated that 'many neurologists would at least hesitate to diagnose FA clinically in the presence of exaggerated deep relexes'. Wilson (1940) admitted that the knee and ankle jerks were usually absent. This has since been confirmed by other authors (Tyrer and Sutherland, 1961; Dyck and Lambert, 1968*b*; Salisachs, 1974), and in nearly all the patients studied the reflexes in the upper limbs were depressed or absent.

Hodge (1897) described three sibs with 'Friedreich's disease all presenting marked increase in the knee jerk', and Sherman (1934) reported two brothers with an illness resembling Friedreich's ataxia but both had increased reflexes. This led Sherman to state that 'this report offers some corroboration of the contention that a spastic form of Friedreich's disease exists'. In a recent study by the present author (Harding, 1981) twenty families with an autosomal recessive disorder similar to, but genetically distinct from, FA were observed. All the patients had normal or increased tendon reflexes; the prognosis was better than that of FA and cardiomyopathy was absent.

Bell and Carmichael (1939) divided 319 cases of hereditary ataxia from published reports into three groups (Friedreich's ataxia, spastic ataxia and spastic paraplegia) based largely on reflex changes. In 35 pedigrees both FA and spastic ataxia were present within the same family. On close examination of the clinical data, it is clear that the majority of these families suffered from diseases very different from FA. In many the age of onset was well over 20 years and inheritance was autosomal dominant in more than half. These families probably had olivopontocerebellar atrophy which can give rise to areflexia in the later stages of the disease (Schut, 1950). It is significant that, in Bell and Carmichael's personally examined series (1939), only two families with FA contained individuals with absent and present reflexes. In fact the authors suggested that loss of tendon reflexes was an early sign in FA; they found areflexia in three young children with incipient disease.

Nevertheless, Bell and Carmichael's data led Roth (1948) to suggest that FA and Marie's (spastic) ataxia were variants of the same disease. This concept was further elaborated by Schut (1950) with very little justification. Roth (1948) also referred to patients with combinations of Friedreich's ataxia and other features. These are not infrequent in the literature and include such diverse syndromes as FA with myopathy (Bing, 1905), myoclonic epilepsy (Hunt, 1921), Leber's optic atrophy (Ferguson and Critchley, 1928), Parkinsonism (Bénard, Grossiord, Gruner and Hoppeler, 1952) and ophthalmoplegia (Stephens, Hoover and Denst, 1958). The definition of Friedreich's ataxia is, to say the least, loose in these reports and few cases bear much similarity to Friedreich's original descriptions. The family reported by Stephens *et al.* (1958) clinically had the features of a mitochondrial myopathy.

Between 1940 and 1970 there were few clinical studies of Friedreich's ataxia. A resurgence of interest in the subject has occurred in the last decade. Skre (1975) found 11 cases of FA in a study of hereditary ataxia in Western Norway. However, his diagnostic criteria must be questioned in some cases as three individuals were stated to have dementia and myoclonic epilepsy in addition to a spinocerebellar syndrome. All developed the disease between the ages of 10 and 14 years. All were dysarthric. Ten had nystagmus, sensory loss and areflexia. In nine the plantar responses were extensor. Six were stated to have a degree of dementia. Salisachs (1974) described the clinical features of 13 patients. The age of onset ranged from 3 to 23 years. Salisachs commented on the high frequency of distal amyotrophy in his cases. An interesting observation was that most of the patients had either pes planus or equino-varus deformity, rather than pes cavus.

Geoffroy, Barbeau, Breton, Lemieux, Aube, Leger and Bouchard (1976) made a serious attempt to define strict diagnostic criteria for FA, stimulated both by the possibility of biochemical investigations into pathogenesis and also previous conflicting reports, for example concerning reflex loss, as to what constitute 'typical signs'. Fifty patients previously diagnosed as FA were assessed by 15 neurologists and assigned to four groups which were: 'complete typical FA' (33 cases), 'incomplete typical FA' (3), 'atypical FA' (6) and 'not FA' (8). It is notable that the 'incomplete' patients (which were all members of one sibship) had had the disease for a shorter period of time than the 'complete' group. Group 3 was thought to represent cases of the Roussy-Lévy syndrome but no nerve conduction studies were performed.

From this study the authors proposed primary and secondary diagnostic criteria for FA. The primary criteria (obligatory for diagnosis) were: onset before the end of puberty (never after the age of 20 years); progressive ataxia of gait; dysarthria; loss of joint position or vibration sense and absent tendon reflexes in the legs; muscle weakness. Secondary features (present in more than 90 per cent) were: extensor plantar responses; pes cavus and scoliosis; cardiomyopathy. This study is commendable, but it is difficult to use the criteria for the diagnosis of early cases (when difficulties arise) as many of the 'obligatory signs' (for example, muscle weakness and sensory loss) may not be present. The mean duration of Geoffroy *et al.'s* 'typical cases' was 12.15 years. One problem which is particularly important in relating their series to other populations is that the patients were a genetically very homogeneous group. They were all French Canadian and it has been estimated (Barbeau, Le Seige, Breton, Coallier and Bouchard, 1976) that the 'original FA gene' was present within a core of 10 families living in Quebec City in the mid-seventeenth century. This virtually represents a genetic isolate which is unlikely to be encountered elsewhere if sufficient patients are available for study.

The present paper presents the clinical and genetic features of 115 patients with Friedreich's ataxia; this is the largest series reported to date. Particular emphasis has been placed on the early features of the disease, in order to facilitate accurate diagnosis at the time of presentation. This is important as diagnostic confusion (such as with cases of HMSN) may lead to misleading prognostic and genetic advice. Furthermore, investigation of metabolic pathways in relation to the underlying disease defect is more appropriate in patients with a relatively short disease duration; it is well-known that physical disability *per se* may lead to biochemical abnormalities such as glucose intolerance (Hewer and Robinson, 1968).

In addition, in view of the genetic homogeneity of the French Canadian series mentioned above, an analysis has been made of variability in the clinical manifestations of Friedreich's ataxia, both within and between sibships and individuals. First degree relatives of patients were also investigated clinically and electrocardiographically in order to establish whether or not there are any heterozygote manifestations of the disease; these have been reported in the Quebec co-operative study (Andermann, Remillard, Goyer, Blitzer and Barbeau, 1976, Cote, Larose, Cimon and Lemieux, 1979).

PATIENTS AND METHODS

The 90 families were investigated as part of a clinical and genetic study of 200 families with progressive cerebellar and spinocerebellar degenerations. The latter families contained 234 index cases which were ascertained from the medical records department of The National Hospitals for Nervous Diseases, The Hospital for Sick Children, Great Ormond Street, other neurological centres in London and the records of the Friedreich's Ataxia Group. Patients were included in the study if they had attended hospital (or were registered with the Friedreich's Ataxia Group) during the period 1966–1980 and lived within a 50 mile radius of central London. Co-operative individuals were visited at home or in hospital by the author. A detailed history was taken to include details of first and second degree relatives. Full neurological and general examinations, twelve-lead electrocardiography and urine testing were performed on the index cases. As many first degree relatives were seen and examined as possible. ECGs and urine tests were also carried out on parents and sibs of patients with Friedreich's ataxia. The results of neurophysiological investigations were obtained from the hospital records of some of the FA patients.

The criteria used for the diagnosis of FA in the index cases were: an age of onset of symptoms before the age of 25 years; progressive unremitting ataxia of the limbs and of gait; absence of the knee and ankle jerks. Dysarthria and extensor plantar responses were important secondary criteria which were found in nearly all the index cases; if these were not present, patients were only included in the study if either they had an affected sib with both signs, or had median motor nerve conduction velocities of greater than 40 $m.s^{-1}$ thus excluding cases of type I HMSN.

RESULTS

One hundred and fifteen patients with Friedreich's ataxia from 90 families were examined, of whom 106 were index cases. Fifty-three patients were male and 62 female; this difference is not statistically significant. The mean age at the time of study was 32.30 ± 13.82 (range 10–73) years. The mean duration of the disease at the time of study was 22.00 ± 12.76 (range 2–61) years.

1. *Clinical Features*

Fig. 1 is a histogram showing the distribution of age of onset of the disorder in these patients. There is no obvious suggestion of bimodality. It will be noted that the majority of cases developed symptoms between the ages of 2 and 16 years; only 4 did so after the age of 20 years. The mean age of onset was 10.52 ± 7.4 (range 1.5–27) years. Ninety-five per cent confidence limits (95 per cent CL) for age of onset were calculated using the formula 95 per cent CL = mean ± 1.96 × standard deviation, which yielded a range of 0–25.02.

The incidence of various presenting symptoms is shown in Table 1. Ataxia of gait was by far the commonest but it is of interest to note that scoliosis and cardiac symptoms were the earliest features in a few patients. One girl, a younger sib of an index case, was asymptomatic but had abnormal signs (truncal ataxia and areflexia) suggestive of FA. This patient will not be included in subsequent analyses as the diagnosis was not definite.

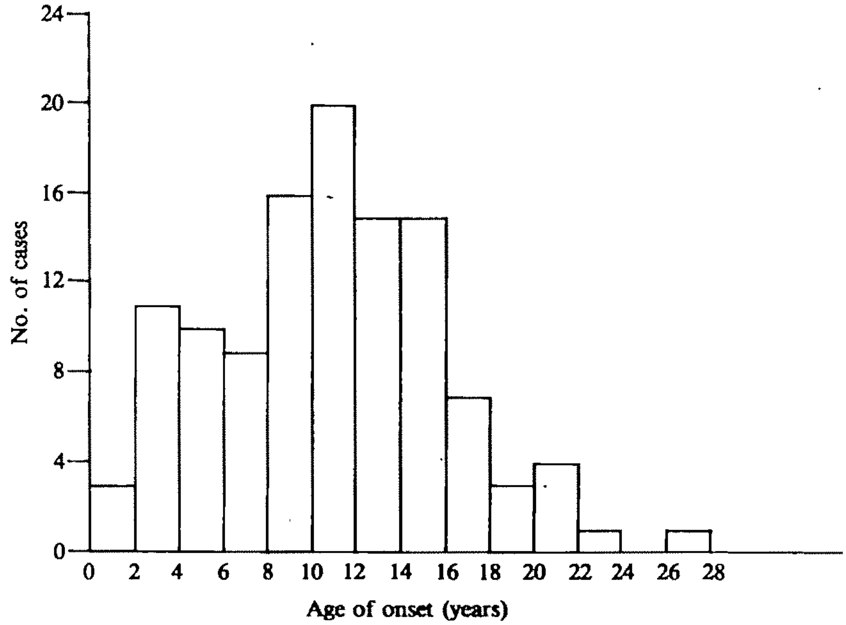

FIG. 1. Histogram illustrating range of age of onset in patients with Friedreich's ataxia.

TABLE 1. FRIEDREICH'S ATAXIA: PRESENTING SYMPTOMS

	No. of cases	%
Ataxia	72	62.6
Generalized clumsiness	29	25.2
Tendency to trip	5	4.3
Scoliosis	6	5.2
Tremor	1	0.9
Cardiac symptoms	2	1.7

The clinical features of these patients are shown in Tables 2–6. Dysarthria was found in nearly all cases; when it was not present, the disease was in its early stages. Nystagmus and deafness occurred in less than half, and titubatory tremor of the head was relatively rare (Table 2). Slow, broken-up pursuit eye movements were observed in a substantial number of patients. Optic atrophy was noted in approximately one-third of cases. This varied from the presence of disc pallor alone, to virtual blindness. In one patient there was mild peripheral pigmentary retinal degeneration; this was not present in her younger sib.

TABLE 2. FRIEDREICH'S ATAXIA: CLINICAL FEATURES

		No. of cases	%
Dysarthria			
Mild		33	28.7
Moderate		53	46.1
Severe		25	21.7
	Total	111	96.5
Titubatory tremor of head		5	4.3
Nystagmus		23	20
Broken-up pursuit eye movements		14	12.2
Optic atrophy			
Disc pallor alone		14	12.2
With mildly reduced acuity		15	13.0
With severely reduced acuity		6	5.2
	Total	35	30.4
Deafness			
Mild		6	5.2
Moderate		2	1.7
Severe		1	0.9
	Total	9	7.8

TABLE 3. CLINICAL FEATURES OF FRIEDREICH'S ATAXIA: SKELETAL DEFORMITY

		No. of cases	%
Scoliosis			
Mild		52	45.2
Moderate		27	23.5
Severe		12	10.4
	Total	91	79.1
Pes cavus			
Mild		33	28.7
Moderate		27	23.5
Severe		3	2.6
	Total	63	54.9
Finger contractures		13	11.3
Knee contractures		3	2.6

TABLE 4. CLINICAL FEATURES OF FRIEDREICH'S ATAXIA

		No. of cases	%
Upper limbs			
Finger-nose ataxia			
Mild		17	14.8
Moderate		51	44.3
Severe		46	40
	Total	114	99.1
Dysdiadochokinesis			
Mild		13	11.3
Moderate		51	44.3
Severe		47	40.9
	Total	111	96.5
Tremor			
Mild		4	3.5
Moderate		2	1.7
	Total	6	5.2
Pyramidal weakness			
Mild		52	45.2
Moderate		18	15.6
Severe		2	1.7
	Total	72	62.5
Distal weakness		10	8.7

TABLE 4 (*continued*)

Upper limbs (continued)		*No. of cases*	%
Distal wasting			
Mild		45	39.1
Moderate		8	6.9
Severe		3	2.6
	Total	56	48.6
Muscle tone			
Normal		88	76.5
Increased		0	0
Decreased		27	23.5
Lower limbs			
Heel-shin ataxia			
Mild		4	3.5
Moderate		20	17.4
Severe		59	51.3
Not testable		32	27.8
Dysdiadochokinesis			
Mild		3	2.6
Moderate		19	16.5
Severe		61	53.0
Not testable		32	27.8
Pyramidal weakness			
Mild		34	29.6
Moderate		35	30.4
Severe		32	27.8
	Total	101	87.8
Distal wasting			
Mild		35	30.4
Moderate		10	8.7
	Total	45	39.1
Generalized wasting			
Mild		17	14.8
Moderate		12	10.4
	Total	29	25.2
Muscle tone			
Normal		83	72.2
Increased		14	12.2
Decreased		18	15.6
Ataxia of gait			
Mild		7	6.1
Moderate		13	11.3
Severe		24	20.9
Not testable		71	61.7

The incidence of various skeletal deformities is shown in Table 3. Scoliosis was by far the commonest; pes cavus (usually mild) occurred in just over half. Finger contractures and knee contractures were relatively rare.

In the upper limbs (Table 4), ataxia was universal. In some patients ataxia could not be detected in the lower limbs because of profound weakness. It will be noted that wasting and occasional weakness of the small hand muscles was present in a high proportion of cases. Distal wasting of the legs was also quite common. Pyramidal weakness of the lower limbs, like dysarthria, was only absent in early cases. Pyramidal weakness of the arms was confined to severely disabled patients. Muscle tone in the limbs was normal in the majority of cases.

Tendon reflex abnormalities (Table 5) are of interest. In over 70 per cent, tendon areflexia was noted. However, in 29 cases one or both biceps jerks were just detectable. In none were they brisk. In one case, the left knee jerk was present but all other reflexes were absent. Plantar responses were extensor in the majority of cases; in only one was a flexor plantar response obtained. This girl's sister had extensor plantar responses. In a few patients the plantar responses were unobtainable.

TABLE 5. CLINICAL FEATURES OF FRIEDREICH'S ATAXIA: REFLEX CHANGES

	No. of cases	%
Tendon reflexes		
All absent	85	74.0
Biceps jerk present	29	25.2
Knee jerk present	1	0.9
Plantar responses		
Extensor	102	88.7
Flexor	1	0.9
Absent	12	10.4

Sensory loss in the lower limbs was common (Table 6). Joint position sense was slightly more frequently affected than vibration sense. Sensory loss in the upper limbs was relatively rare, and again tended to occur in the later stages of the disease.

A few patients had abnormal pain and light touch sensation. Four of these cases were diabetic and so could have had a diabetic neuropathy in addition to Friedreich's ataxia.

At the time of study, 83 patients were chair-bound, that is, they could not walk at all or could take one or two steps with considerable assistance. The mean age of becoming chair-bound (continuously, not just out of doors or for long distances) was 25.14±15.5 (range 11–58) years. The mean 'course' of the disease (age wheelchair-bound minus age of onset) was 15.51±7.41 (range 3–44) years. Figs. 2 and 3 show the distributions of these parameters.

TABLE 6. CLINICAL FEATURES OF FRIEDREICH'S ATAXIA: SENSORY LOSS

Sensory impairment		*Upper limbs* *No. cases (%)*	*Lower limbs* *No. cases (%)*
Vibration sense			
Mild		14 (12.2)	33 (28.7)
Moderate		1 (0.9)	51 (44.3)
	Total	15 (13.0)	84 (73.0)
Joint position sense			
Mild		24 (20.9)	46 (40.0)
Moderate		3 (2.6)	44 (38.3)
	Total	27 (23.5)	90 (78.3)
Light touch			
Mild		4 (3.5)	7 (6.1)
Moderate		0	3 (2.6)
	Total	4 (3.5)	10 (8.7)
Pain			
Mild		6 (5.2)	5 (4.3)
Moderate		0	4 (3.5)
	Total	6 (5.2)	9 (7.8)

As the distributions were not normal 95 per cent confidence limits were not calculated. Nevertheless, it is clear from the histograms that over half of the cases were chair-bound sixteen years after the onset of symptoms (or aged about 26 years); over 95 per cent had stopped walking by the age of 44 years, i.e., approximately thirty-five years after onset.

The mean duration of the disease in patients not chair-bound was 11.0 ± 6.8 (range 2–30) years. The mean age of death in sibs who had died (excluding accidental death or suicide) was 37.54 ± 14.35 (range 21–69) years.

2. *Progression of Friedreich's Ataxia*

It is generally not difficult to make a diagnosis of FA in cases of long duration; in early cases, it may not be straightforward. In order to establish which clinical features are present early in the course of the disease, the patients were split into groups depending on duration of symptoms and the percentage demonstrating various physical signs was calculated for each group. It was felt that this sort of analysis should be useful in determining whether a particular feature, for example, wasting of the hands, is present early in some cases or if it is a late manifestation which may develop eventually in all patients. The results are shown in fig. 4, as histograms with the percentage of patients having the particular clinical feature plotted against duration of disease. Correlation coefficients are shown on the right-hand side of the figures. The last two cells (duration 55 to 65 years) are probably rather unreliable as they only represent three cases.

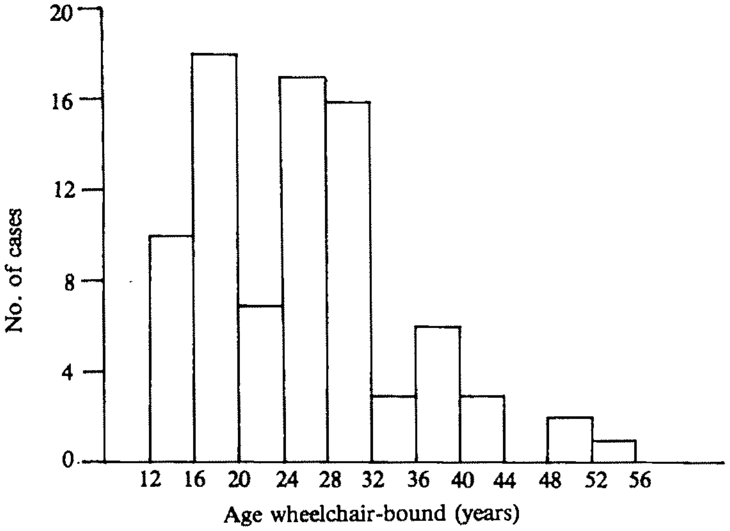

FIG. 2. Histogram illustrating range of age of becoming chair-bound in patients with Friedreich's ataxia.

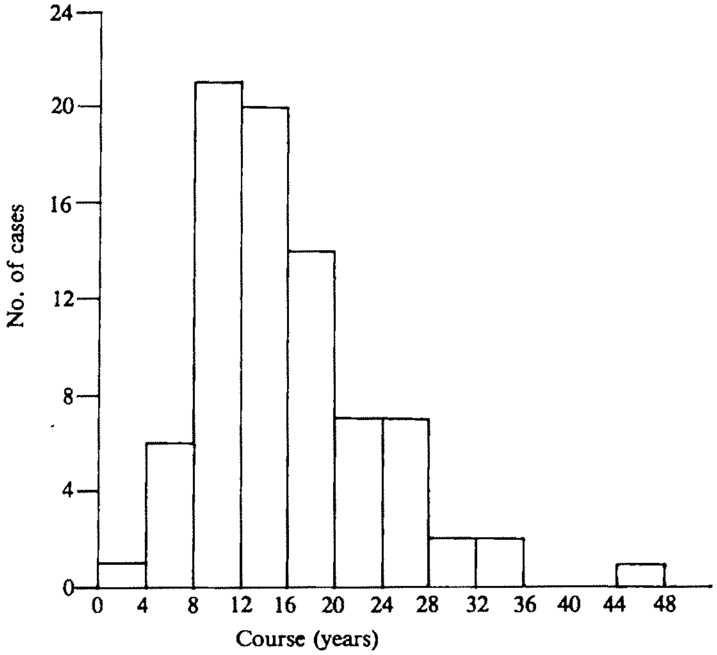

FIG. 3. Histogram illustrating range of 'course' (age chair-bound minus age of onset) in patients with Friedreich's ataxia.

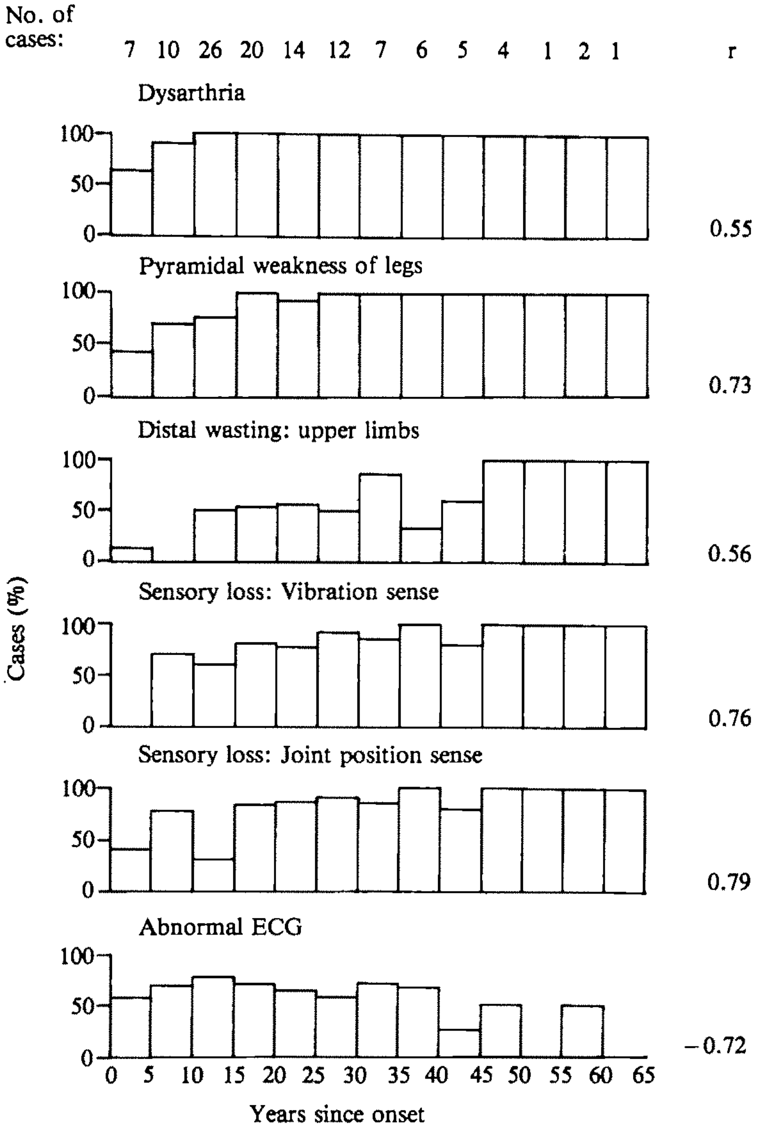

FIG. 4. Histograms illustrating incidence of various physical signs in relation to duration of disease in patients with Friedreich's ataxia (r = correlation coefficient for percentage against duration).

It will be noted that dysarthria was present in nearly 60 per cent of cases five years after the onset, but it was found in all cases after ten years. Pyramidal weakness of the legs showed a similar pattern. Wasting of the hands showed some correlation with duration but this was not as marked as for some of the other features.

Sensory loss was not such an early sign as dysarthria or paraparesis but achieved near 100 per cent levels after twenty-five years. Joint position sense loss appeared to be an earlier sign than reduction of vibration sense; nearly 50 per cent of cases in the first five years of the disease had abnormal joint position sense whereas none had loss of vibration sense.

The percentage of cases with abnormal electrocardiographic changes was fairly constant until disease duration was more than forty years; the proportion was then somewhat less. Correlation with duration was significantly negative.

Important clinical features not analysed in this way were tendon reflex changes or limb and gait ataxia. These signs were present in every patient studied, including the asymptomatic one mentioned earlier and all the secondary cases. Extensor plantar responses were found in all patients (except the asymptomatic case) who had had symptoms for less than five years, although other pyramidal signs were not.

Ideally, in attempting to delineate early signs of Friedreich's ataxia, one should preferably analyse very early cases, perhaps those with symptoms for less than two years. Unfortunately, in this study, there were only two such cases, plus the asymptomatic one mentioned above. Only one had dysarthria and pyramidal weakness of the legs. None had any sensory loss.

3. *Neurophysiological Investigations*

Twenty-nine patients had had nerve conduction studies performed. Values for median motor nerve conduction velocity (MNCV) were available in 22 instances; the mean was 52.20 ± 7.63 $m.s^{-1}$. This is significantly lower than that of a control series of 57.2 ± 4.2 $m.s^{-1}$ (Thomas, Sears and Gilliatt, 1959) ($t = 2.82, P < 0.01$). The mean peroneal MNCV from 22 patients was 44.96 ± 7.20; this is also lower than that of controls but not quite significant at the 5 per cent level (49.7 ± 7.1, $t = 1.95$, $P < 0.1 > 0.05$).

Sensory nerve conduction studies had been performed in 26 cases; in 24 at least one sensory action potential (usually all) was absent. In one patient the sensory action potentials were reduced in amplitude. In one other sensory action potentials were normal, both in amplitude and latency, but a spinal somatosensory evoked response was absent. Only 2 of the patients who had had symptoms for less than five years had been subjected to sensory conduction studies; sensory action potentials were absent in both.

4. *Other Features*

(*a*) *Cardiomyopathy*. A total of 46 patients had cardiac symptoms. All had dyspnœa on exertion (of whom seven had normal ECGs); 13 had palpitations and 4 angina (all with abnormal ECGs).

Signs of cardiac disease were observed in about 10 per cent of cases. Cyanosis of the feet was noted in nearly half. This, together with hypertension and ankle œdema, occurred in patients with or without electrocardiographic incidence of cardiomyopathy (but predominantly the former). Cardiac murmurs (nearly all apical or left sternal edge systolic ejection bruits) and clinical cardiac enlargement were relatively common; frank cardiac failure was present in only one patient.

Electrocardiographs were recorded in 114 patients. Twenty-eight were normal. In the 86 abnormal records T-wave changes and right or left ventricular hypertrophy were the commonest findings. Conduction disturbances and constant dysrhythmias were rare. More patients had supraventricular than ventricular extrasystoles. Eleven of these ECGs showed changes which were thought to be insignificant (axis changes of less than 30 deg, left ventricular hypertrophy if R in lead V_5 and S in lead V_1 amounted to less than 60 mm, and minor anti- or clockwise rotation).

(*b*) *Diabetes*. Twelve patients were known to be diabetic. None of the other cases was found to have glycosuria. Another 2 patients not seen were stated to have had diabetes. The mean age of onset of diabetes was 25.0 ± 10.64 years. The mean duration of neurological disease at the time of onset of diabetes was 15.5 ± 6.82 years. Seven patients presented with polyuria and polydipsia, 3 diabetic pre-coma and one pruritus vulvæ. One patient made the diagnosis himself by urine testing. Nine of the 12 patients were insulin-dependent although one of these had been controlled on oral hypoglycæmic drugs before requiring insulin. The mean age of onset of diabetes and duration of disease at time of onset were significantly lower in the insulin dependent diabetics than those on oral hypoglycæmic drugs. (Age of onset (years): insulin dependent: 21.0 ± 8.72; oral hypoglycæmic drugs: 37.0 ± 5.92, $t = 2.94$, $P < 0.02$; duration of disease (years): insulin dependent: 13.11 ± 6.07; oral hypoglycæmic drugs: 22.67 ± 2.31, $t = 2.59$, $P < 0.05$).

Five of the diabetics were poorly controlled, as judged by the presence of 2 per cent glycosuria more than twice weekly. Two patients had had episodes of ketoacidotic coma. The mean dose of insulin required was 52.0 ± 20.5 units. The dead sib known to have been diabetic had died as a result of ketoacidotic coma. No diabetic patient had clinical evidence of retinopathy. Four had sensory loss suggesting diabetic neuropathy in addition to the underlying neurological disease.

5. *Genetic Considerations*

Apart from the 106 index cases, 9 relatives were seen and found to be affected. In addition, 29 other relatives (27 sibs and 2 cousins) were stated to be affected but were unavailable for study. Fifteen of these (14 sibs and one cousin) were dead. Thirty-eight other sibs were examined and found to be normal. It is unlikely that any other sibs (stated to be normal) were actually affected as the majority were well past the age at risk of developing the disorder. Fifty-eight parents of affected individuals were examined and were neurologically normal; one father had slight clawing of the toes. Thirty-five patients were or had been married; 15 of these (8 males and 7 females) had had a total of 32 children (18 born to males and 14 to females). Four of these children were examined and found to be normal. Two other patients had had illegitimate children, neither of which was seen.

In only one instance did an affected individual have affected offspring. This family has been reported in detail elsewhere (Harding and Zilkha, 1981) and it was thought that it was an example of 'pseudo-dominant' inheritance, i.e., a homozygote-heterozygote mating occurred. In 5 families there were more remote affected relatives. These were as follows: 3 first cousins once removed; one great-niece; and one third cousin. There were no pedigrees suggestive of X-linked inheritance if sibships with one or more affected boys are excluded.

The pedigree data therefore suggest autosomal recessive inheritance. Segregation analysis was performed on all sibships (excluding the 'pseudo-dominant family) using Weinberg's proband method (Weinberg, 1927). As there were very few sibs still at risk of developing the disease, and nearly all were examined by the author and found to be normal, a correction factor for age of onset was not thought to be necessary. The Weinberg proband method is a direct calculation of the proportion of affected sibs of index cases and the method is self-correcting regardless of whether ascertainment is single, multiple or truncate (Crow, 1963). This yielded a value for P ($=$ segregation ratio) of 0.255. The standard error (SE) of P was calculated from the formula $\mathrm{SE} = \frac{P(1-P)}{n}$ where $n =$ total number of sibs of index patients. The SE was 0.027, giving 95 per cent confidence limits ($P \pm 1.96 \times \mathrm{SE}$) of 0.202–0.307. Weinberg's proband method assigns too much weight to large families and not enough to small families (Crow, 1963). An improved estimate of P and its variance was therefore calculated using a correction factor for family size. Each family size estimate was multiplied by C, where $1/C = 1+\pi+P\pi(s-3)$, $\pi =$ ascertainment probability, $P = 0.255$ and $s =$ sibship size. The improved estimate of P ($\hat{P}$) was given by $\hat{P} = \frac{\Sigma Ca(r-1)}{\Sigma Ca(s-1)}$, where $a =$ number of probands in the sibship and $r =$ number of affected persons in the sibship. The variance of $\hat{P}$ was given by the expression $\frac{\hat{P}(1-\hat{P})}{\Sigma Ca(s-1)}$ (Crow, 1963). These calculations yielded a value of $\hat{P}$ of 0.267, SE of 0.034 and 95 per cent confidence limits of 0.199–0.333. The values of P and $\hat{P}$ are not significantly different from 0.25, therefore supporting autosomal recessive inheritance.

Further evidence for this was provided by the consanguinity rate amongst parents of affected individuals: this was 5.55 per cent (five families); all of these were English first cousin marriages.

6. *Variation Within and Between Families and Individuals*

It became clear during the course of this study that there was perhaps somewhat more variation in clinical features and the course of the disease between individuals than might be expected in an autosomal recessive disorder. Sib pairs, however, tended to be similar in this respect. In a previous communication (Winter, Harding, Baraitser and Bravery, 1981) the results of estimations of intrafamilial correlation of age of onset and age of losing the ability to walk independently were presented, using data from this study and some other families. These suggested that

Friedreich's ataxia may be genetically heterogeneous but the evidence was not conclusive.

The possibility of genetic heterogeneity was also investigated by examining concordance of the presence of diabetes and cardiomyopathy within sibships. For cardiomyopathy, two analyses were performed. A product-moment correlation coefficient of QRST angle (the angle between the QRS and T-wave axes which is a sensitive index of abnormal repolarization (Schamroth, 1976)) between sibs was calculated using data from 16 sibships. This yielded a value of r of 0.303 ($P > 0.05$). Analysis of variance suggested that variation between sibships was just significantly greater than that within sibships ($F = 2.55$, $P > 0.025$). A corrected value of r using Donner and Koval's method of computing correlation coefficients (1980) was 0.49 ($P < 0.05$).

In addition, the hypothesis that cardiomyopathy was distributed randomly amongst individuals with Friedreich's ataxia was tested using a χ^2 test. Expected values were calculated from the probabilities (based on percentages from the total number of patients) of any combination of normal/abnormal ECGs in the sibships available for study. The result is shown in Table 7. It is highly significant, in favour of the presence or absence of cardiomyopathy being concordant within most families although there were four sib pairs in which one had an abnormal ECG and the other (the elder in all instances) was normal. In the three families where there were affected members on whom ECGs were performed in more than one sibship, cardiomyopathy was either present or absent in all affected members of these kindreds.

TABLE 7. FRIEDREICH'S ATAXIA: DISTRIBUTION OF CARDIOMYOPATHY AND DIABETES WITHIN SIBSHIPS

		No. of sibships	
Index sib/others		*Observed*	*Expected*
Cardiomyopathy			
+/−		0	4.20
+/+		9	8.53
−/+		4	4.20
−/−		6	2.07
	Total	19	19
χ^2		8.96	
P		< 0.01	
Diabetes			
+/−		1	3.21
+/+		3	0.38
−/+		1	3.21
−/−		29	27.2
	Total	34	34
χ^2		13.71	
P		< 0.001	

The same procedure was followed for diabetes (*see* Table 7) and the result was highly significant, suggesting a strong tendency for diabetes to cluster within families, 42.8 per cent of affected sibs of patients with diabetes were also diabetic.

Clustering of various clinical features in individuals was also examined; these were optic atrophy (with visual acuity of less than 6/12), deafness, diabetes and cardiomyopathy. Expected values were calculated by using the percentage incidence of the clinical features in all patients as probabilities. For instance, the incidence of diabetes and optic atrophy with reduced visual acuity was 10.43 and 18.26 per cent, respectively; therefore the probability of an individual having diabetes and optic atrophy is $0.1043 \times 0.1826 = 0.0190548$. This value multiplied by the total number of cases gives the expected number of cases with both features. The results of analyses investigating the associations of optic atrophy and diabetes, optic atrophy and deafness, diabetes and cardiomyopathy and severe scoliosis and cardiomyopathy are shown in Table 8. It will be noted that there is highly significant clustering of the first two combinations of clinical features within individuals.

TABLE 8. FRIEDREICH'S ATAXIA: DISTRIBUTION OF CLINICAL FEATURES WITHIN INDIVIDUALS

Combination	χ^2	*P*
Optic atrophy/diabetes	6.83	< 0.01
Optic atrophy/deafness	9.87	< 0.01
Diabetes/cardiomyopathy	3.36	> 0.05
Severe scoliosis/cardiomyopathy	3.57	> 0.05

7. *Investigation of Near Relatives*

A total of 101 unaffected first degree relatives of patients with Friedreich's ataxia were examined. Fifty-eight were parents, 38 sibs and 5 children of affected individuals. One sib had a mild hemiplegia subsequent to a stroke. One father had clawing of the toes but no obligate heterozygote had frank pes cavus or any other skeletal abnormality. The remaining 99 (of whom 61 were obligate heterozygotes) were neurologically normal. Several parents and sibs had mild hypertension. One father, in addition to hypertension, was found to have signs of aortic incompetence.

ECGs were performed on 38 heterozygotes (37 parents and one child), and 8 normal sibs. Thirty-two of these were normal. Seven had mild left ventricular hypertrophy alone, including one with hypertension. Two had significant left axis deviation. Two had right axis deviation, including one with multiple ventricular ectopics. Two patients had left ventricular hypertrophy and strain patterns, both of whom were hypertensive, including the male with aortic incompetence mentioned above. One heterozygote had minor T-wave abnormalities; she was known to be hypertensive. No heterozygote or normal sib had frank changes of cardiomyopathy similar to that found in the FA patients.

None of the heterozygotes or siblings examined was a known diabetic and none had glycosuria. A history of diabetes was obtained in the father of one sibship; none of his normal offspring was diabetic. There was a family history of diabetes in 8 second-degree relatives of 7 index cases, of whom 2 were diabetic. All these relatives had diabetes of maturity onset; 6 of them were grandparents of index cases. The incidence of diabetes in grandparents of non-diabetic patients was 1.62 per cent and, of diabetic patients, 1.92 per cent.

DISCUSSION

1. *Clinical Features*

The range of ages of onset in FA was high for an autosomal recessive disorder, but it corresponds to those found by other authors (Mollaret, 1929; Wilson, 1940; Sjögren, 1943; Tyrer and Sutherland, 1961). Geoffroy *et al.* (1976) considered that true Friedreich's ataxia must always be clinically manifest before the end of puberty, and at the very latest before the age of 20 years. This is a reasonable general rule, but the present study indicates that exceptions do occur. Exact age of onset is difficult to establish, especially when patients are first seen at a relatively advanced stage of the disease. All of the patients described here in whom the age of onset was 20 years or over had had symptoms for more than ten, and usually over twenty, years. The mean duration of disease in the whole series was ten years higher than that reported by Geoffroy *et al.* (1976). The presenting symptoms noted in this study confirm that the initial complaint may be in relation to skeletal deformity or cardiac disease (Smith 1885; Whyte, 1898; Berg, Kaplan, Jarrett and Molthan, 1980). Two of the patients in this series had been diagnosed as having hypertrophic cardiomyopathy prior to the development of neurological symptoms. Cardiomyopathy is not common in children and teenagers; its presence should demand full neurological assessment before invasive investigations are undertaken.

It is clear from this study that ataxia in all four limbs and of gait, and absent tendon reflexes in the lower limbs, are mandatory for the diagnosis of FA. Dysarthria was not present in all cases of recent onset. There have been very few studies of the clinical features of early cases of FA. Friedreich (1863*c*) considered that dysarthria was an early sign, and Geoffroy *et al.* (1976) 'found it present within the first two years of evolution' in all their patients. The authors do not mention how many had had symptoms for less than two years, and, as the total number was relatively small (33), with a mean duration of 12.5 ± 7.13 years, this statement may be viewed with caution. In the patients studied by Dunn (1973), dysarthria was absent at six months, three and four years after onset in 3 cases.

The finding of relative preservation of the biceps jerks in some patients in this series is of interest; this has not been observed by other authors. This is presumably due to integrity of the reflex arc in higher cervical segments which would correlate with the fact that degeneration of afferent fibres in the spinal roots is most severe caudally (Friedreich, 1876). This study has confirmed that areflexia in the lower limbs is a *sine qua non* in FA (it was found in all the secondary cases in this series) and supports the view of Tyrer (1975) that the diagnosis should not be made if the tendon reflexes are increased.

Geoffroy *et al.* (1976) found extensor plantar responses in all their patients except two, both of whom had had symptoms for less than one year. The plantar responses were flexor in only one established case in the current series; they were extensor in her sister. The plantar responses were extensor in all patients with disease duration of less than five years, but flexor in the asymptomatic patient. In nearly all the individuals who had absent plantar responses, the disease was of long duration, usually more than thirty years. Others had been subjected to surgical treatment. It seems reasonable to suggest that extensor plantar responses are of major importance in the early diagnosis of symptomatic patients with FA.

Geoffroy *et al.* (1976) considered muscle weakness and posterior column sensory loss to be obligatory diagnostic criteria. The present study does not confirm this view, and neither do those of other authors (Saunders, 1913; Dyck and Lambert, 1968*b*; Salisachs, 1974). Joint position sense (the most frequently lost modality) was abnormal in only half of the patients who had had symptoms for less than five years, and normal in a few in whom the disease was well established. The explanation of apparently abnormal pain and temperature appreciation in the small number of patients who were not diabetic is difficult. Saunders (1913) observed similar abnormalities in a minority of patients, and suggested that this was due to reduced skin temperature. This view may well be correct; the patients with cutaneous sensory loss in this series were all chair-bound and most had marked cyanosis of the feet. It also would not be particularly surprising to find subjective sensory impairment in 6 out of 115 normal individuals. However, it is possible that in more advanced cases there is some loss of smaller dorsal root ganglion cells.

Pyramidal weakness of the legs was universal in this series only after the disease had been present for twenty-five years or more; it was present in half of those in the early stages of the disorder. Thus its absence does not exclude a diagnosis of FA. It was not found in the 'typical incomplete' patients in the series of Geoffroy *et al.* (1976), who had been symptomatic for fewer years than the 'typical complete group'. The separation of these two groups seems rather artificial and confusing, as the most likely explanation for the 'incompleteness' is that these were early cases in which the fully developed clinical picture had not yet evolved. The normal muscle tone found in the presence of pyramidal weakness in the majority of patients in the present study is in accordance with the findings of Wilson (1940). This is presumably due to deafferentation of muscle spindles from loss of the larger dorsal root ganglion cells.

The presence of distal wasting and, in some cases, weakness requires comment. The incidence in this study (about 50 per cent) would not support the contention of Symonds and Shaw (1926) that distal amyotrophy never occurs in FA. Wasting in the lower limbs may have been in part due to disuse as it was commoner in the late cases but it was also present in the hands in a considerable number of patients in the early stages of the disease. Gilbert (1962) stated 'when distal muscular atrophy develops in the course of what might have appeared to represent FA, that diagnosis should be seriously questioned'. In Gilbert's family onset was relatively late (around the age of 18 years), and the patients did not become chair-bound until their mid-forties. These points led the author to suggest that they had a different disease. It is true that the histogram shown in fig. 4 could be produced if this series were contaminated by some patients with marked amyotrophy in whom the course of the disease was relatively slow. Two of the oldest patients studied had marked wasting of the small hand muscles. Nevertheless, amyotrophy was not uncommon in the early stages of the disorder, and this has been observed by other authors (Whyte, 1898; Salisachs, 1974). Friedreich (1876) and Spiller (1910) considered it to be frequent in the late stages of the disease. There was not a great deal of evidence for genetic heterogeneity in the present series. The explanation, on a pathological basis, for amyotrophy in FA is not absolutely clear; there have been conflicting reports concerning the presence or absence of anterior horn cell degeneration at autopsy (Mackay, 1898; Oppenheimer, 1979) and no extensive electromyographic studies have been performed.

Although formal testing of intellectual function was not undertaken in this study, it is notable that dementia was not obvious in any of the patients seen, given that many of them were chronic invalids and had little in the way of intellectual stimulation. This would be in keeping with the findings of Davies (1949) who found no difference in IQ between patients with FA and other individuals with longstanding physical disability. Although Bell and Carmichael (1939) suggested that dementia was common, it is clear that their material was clinically and genetically heterogeneous.

The incidence of nystagmus in this series was not high (20 per cent) compared with those of other authors (Friedreich, 1863*b*; Mollaret, 1929). Gilbert (1962) considered that nystagmus was invariably found in patients with FA. Geoffroy *et al.* (1976) observed it in 42.2 per cent of their 'complete' group and a smaller proportion in the 'incomplete' one. The occurrence of broken-up, jerky pursuit eye movements in the current series is interesting. These are probably more frequent than is obvious clinically; Kirkham, Guitton, Katsarkas, Kline and Andermann (1979), using electro-oculography, observed inability to pursue targets moving at velocities of 18 deg/s without the use of multiple small 'catch-up' saccades in 12 out of 14 patients.

One of the patients had mild peripheral pigmentary retinal degeneration; this was not present in her affected younger brother or cousin. This has not been described before in association with typical FA. The patient in question had otherwise typical neurological signs, plus cardiomyopathy and diabetes. Serum lipids were normal, thus excluding abetalipoproteinæmia.

The incidence of optic atrophy (about one-quarter of cases) is higher than the proportion (12 per cent) reported by Sjögren (1943); it is similar to that observed by Geoffroy *et al.* (1976). In the patients with optic atrophy, one-third had preserved visual acuity. The work of Carroll, Kriss, Baraitser, Barrett and Halliday, who examined visual evoked potentials in patients with FA and found abnormalities in 64 per cent (1980), would suggest that sub-clinical involvement of the visual pathway is common in FA. The significant association of optic atrophy with deafness and diabetes is of interest. This triad of clinical features has been observed without other neurological disease as an autosomal recessive disorder (Rose, Fraser, Friedmann and Kohner, 1966). The association of FA, diabetes and optic atrophy was reported by Schlezinger and Goldstein (1940), Ashby and Tweedy (1953) and Podolsky, Pothier and Krall (1964). In all these patients and those from the present study there were no signs of diabetic retinopathy. It seems most likely that the explanation for these associations is related to the presence of modifying genes.

Scoliosis was present in nearly 80 per cent of the patients examined. This frequency is close to that reported in Friedreich's (1876) original descriptions, and those of other authors (Barrett, 1927; Mollaret, 1929). It was more common in patients who developed symptoms before the age of 12, and was often rapidly progressive during growth spurts; Geoffroy *et al.* (1976) made similar observations. These authors found a higher incidence of scoliosis (90 to 100 per cent) in their series but it was diagnosed radiologically in some instances. In the same report, pes cavus deformity was noted to be virtually universal. All of Salisach's (1974) cases were noted to have foot deformity, but several had pes planus or equino-varus deformity as opposed to pes cavus. In the present study, foot deformity was only present in just over half of the cases. It is easy to over-diagnose mild pes cavus, particularly in a disorder where the term 'Friedreich foot' has arisen. Pes planus and equino-varus deformity were not common in this series; the distinction of the latter from pes cavus is important, particularly if surgery is contemplated.

The disease was gradually progressive in the patients described here, although some felt that it had become relatively static once they had become chair-bound. This is more likely to be due to less testing physical circumstances rather than lack of progression. The mean age of losing the ability to walk independently, and the 'course', were similar to those suggested by Dyck and Lambert (1968*b*) and Salisachs (1974); they are a considerable improvement on the figures given by Greenfield (1954) who suggested that many patients were chair-bound five years after onset. The mean age of death in the present study was almost identical to that observed by Hewer (1968). Caution should however, be exercised in using these figures in prognosis, as they naturally apply only to patients who have died, and take no account of those still alive. As the mean age at the time of study in this series was 32.3 years, many must survive the fourth decade.

The results of neurophysiological investigations from this study are similar to the findings of McLeod (1971) and others. McLeod reported somewhat lower (mean 36.8 ± 3.6 m.s^{-1}) peroneal MNCV than was observed in the present series. All the patients had absent or small sensory action potentials except one in this study. It is of interest that the latter had an absent spinal evoked response; the patient had had symptoms for seven years. It is possible that the spinal evoked response is a more sensitive test of abnormal sensory conduction than the production of sensory action potentials by digital nerve stimulation. This would suggest that degeneration of the presynaptic fibres in the posterior horns occurs before that of the peripheral sensory axons. Nevertheless, some of the patients had a shorter duration of disease at time of study than the one mentioned above and had abnormal sensory action potentials. The latter have been reported in early cases by Dunn (1973). Abnormal sensory conduction appears to be a useful diagnostic criterion in FA.

2. *Cardiac Features*

The incidence of cardiac signs and symptoms in FA was surprisingly low in view of the high frequency of ECG changes. Similar clinical features have been observed by other authors (Heck, 1963; Thoren, 1964). The proportion of patients with abnormal ECGs has varied considerably in previous reports (from 30 to 90 per cent), mainly due to differences in neurological diagnostic criteria (Evans and Wright, 1942; Thoren, 1964). Malo, Latour, Cote, Geoffroy, Lemieux and Barbeau (1976) reported significant T-wave abnormalities in 18 out of 32 patients with 'typical' FA and 'probably significant' minor abnormalities in another 4. These findings are very similar to those of the present series. The cause of the associated cardiomyopathy in FA is unknown. Various hypotheses have been proposed, including overactivity of the sympathetic nervous system (Guillain and Mollaret, 1932) and intracardiac arterial disease (James and Fisch, 1963). Both these suggestions have been refuted (Urich, Norman and Lloyd, 1957; Hewer, 1969). Evans (1949) suggested that the cardiomyopathy was a primary disease of cardiac muscle, similar to that found in 'familial cardiomyopathy'). Manning (1950) postulated that the association of FA and cardiomyopathy might be due to genetic linkage of the two disorders but this has not been borne out; there have been no reports of sibs or parents with frank cardiomyopathy in the absence of neurological disease, and there was none in this study. It is most likely that the association of cardiomyopathy with FA is due to the effects of a pleiotropic gene. Although there was a tendency for cardiomyopathy to cluster within families in this series, and similar findings were described by Thoren (1964) and Malo *et al.* (1976), there were several instances of discordance. These could not be explained in terms of age as it was always the older sib who had a normal ECG. These discrepancies could either be due to incomplete penetrance of certain effects of a pleiotropic single gene or, more probably, to different modifying genes.

3. *Diabetes*

The incidence of diabetes mellitus in the patients seen in this study (10 per cent) was similar to that reported by Hewer and Robinson (1968) but slightly lower than that in Thoren's (1962) cases. The diabetics in this series developed diabetes at a similar mean age to those of Thoren's, and had had neurological symptoms for an almost identical mean period. In both this study and others in the literature the onset of diabetes was always after the development of the neurological disorder. The age of onset of diabetes in Hewer and Robinson's (1968) series was considerably later; most were over 40 years. Diabetic control was noted to be poor in the current study on the whole; this was likely to be as a result of imperfect management. The patients with persistent glycosuria rarely attended diabetic or neurological clinics or had blood glucose estimations performed. This was mainly because of their limited mobility. It is probably unreasonable to suggest that patients with a progressive neurological disorder should achieve near perfect control of their diabetes, but some experienced discomforts such as thirst and pruritus as a result of hyperglycæmia. Two had required hospital admission for episodes of ketoacidosis.

It is of interest that in 25 per cent of the patients in this series diabetes was controlled by oral hypoglycæmic drugs rather than insulin, and that the mean age of onset of diabetes was later in these cases than the insulin-dependent ones. There have been few previous reports of non-insulin-dependent diabetes in FA. Hewer (1968) noted that 16 out of 18 known diabetics required insulin. The insulin requirements of the other patients in the current study were moderately high, as were those reported by Thoren (1962). Over half of the patients reported by Hewer and Robinson (1968) only required 20 units of insulin per day; all had developed diabetes over the age of 35 years. It is quite probable that a higher proportion of patients with FA and diabetes could be controlled on oral hypoglycæmic drugs than is supposed. There has been a tendency in the past to assume that all young diabetics are insulin-dependent; this has led to the only relatively recent major recognition of 'maturity-onset diabetes of youth' (Renold, Mintz, Muller and Cahill, 1978).

All the diabetics in this series except one had ECG evidence of cardiomyopathy although there was no significant clustering of the two features. Similar observations were made by Thoren (1962) and others. It is likely that the increased incidence of diabetes in FA is due, like cardiomyopathy, either to pleiotropy or alteration of the effects of the main gene by modifiers. Whether or not glucose intolerance is secondary to a primary defect of metabolism is unknown. There has been some debate as to the site of the defect in glucose utilization (Joffe, Segal and Cooper, 1973; Shapcott, Melancon, Butterworth, Khoury, Collu, Breton, Geoffroy, Lemieux and Barbeau, 1976); this warrants further study.

It is possible that a third of the diabetics in this study had a peripheral neuropathy due to diabetes superimposed on their neurological disease. This assumption is based on clinical findings alone, as neurophysiological investigations would not be helpful in this instance. None had features of autonomic dysfunction or signs of other complications such as retinopathy or proteinuria. There have been no previously published reports of diabetic retinopathy, neuropathy or nephropathy in patients with FA.

Like cardiomyopathy, diabetes is a major cause of morbidity and mortality in FA. A brother of one of the index cases in this study had died in diabetic ketoacidosis which was only diagnosed shortly before death. In Hewer's (1968) series of fatal cases, 4 had terminal ketosis, one of which was undiagnosed in life.

Four patients were diagnosed as having diabetes in the last month of life. Hewer concluded: 'It is important to actively exclude diabetes in patients with FA, particularly when they become unwell.'

4. *Genetic Aspects*

Apart from the family with 'pseudo-dominant' inheritance the pedigree data from these families with Friedreich's ataxia suggested that the disease is produced by an autosomal recessive gene. This was supported by a segregation ratio very close to 0.25 and an increased consanguinity rate amongst parents of affected individuals. The finding of affected cousins or other distant relatives in five families is not incompatible with recessive inheritance, even in the absence of consanguinity. The heterozygote frequency in FA is about 1 in 110 (Harding and Zilkha, 1981), so the probability of an individual first cousin once removed of an index case being affected is 1 in 1760. This probability is clearly very small, but its occurrence should not be unexpected.

The clustering of cardiomyopathy and diabetes within sibships demonstrated in this study has some practical value. The probability of an affected sib of a diabetic patient developing diabetes is high enough (0.43) to warrant, at least, annual or six-monthly urine testing or blood sugar estimations. The presence of cardiomyopathy or diabetes also has prognostic significance; most of the longest survivors in this series had normal ECGs and were not diabetic.

Clinical similarities between members of the same sibship have been noted before in FA. Soca (1888) stated: 'Friedreich's disease commences at the same age, within two or three years, in all members of the family which it attacks'. Marie (1892) commented that FA exhibited 'special traits' within families. Bouchard, Barbeau, Bouchard, Paquet and Bouchard (1979) studied 8 sibships containing 19 affected individuals in an isolated area of Quebec. It was shown all these patients were descended from a single couple who married in 1786. Inbreeding was frequent in the community. Nearly all the patients developed symptoms between the ages of 5 and 8 years, and most were in wheelchairs in their mid-teens. Flexor spasms, myopia, urinary symptoms, reduced pain appreciation and dysphagia were all common; most of these features are rare in FA. All except one had an abnormal ECG. Clearly the main gene giving rise to the disorder was identical in all these cases; their specific features and marked similarity were presumably due to the presence of the same modifying genes. As has been mentioned, the genetic homogeneity of the French Canadian cases as a whole makes them difficult to compare with the present series.

This study has failed to demonstrate the presence of any manifestations of the disorder in heterozygotes. None had any abnormal neurological signs that could not be explained on the basis of other pathology, and none had any significant skeletal abnormality. It is highly probable that some of the reports of pes cavus occurring in relatives of patients with FA relate to asymptomatic cases in families with Charcot-Marie-Tooth disease misdiagnosed as Friedreich's ataxia. Some of the abnormalities described by Andermann *et al.* (1976), such as depression of the ankle jerks, are rather subjective. Similarly, there have been no convincing descriptions of clear-cut ECG abnormalities, such as those found in FA, in heterozygotes. All of the changes identified in this series were compatible with underlying hypertension, ischæmic heart disease or recognized normal variations. The same applies to previous studies (Thoren, 1964: Andermann *et al.*, 1976; Cote *et al.*, 1979).

The incidence of diabetes in close relatives in the current study was not higher than would be expected in the normal population. There can be few individuals who do not have a close or distant relative with diabetes of maturity onset. There have been no studies reported where the incidence of diabetes in relatives with FA has been compared with that of controls. Thoren (1962) found that diabetic patients with FA more frequently had diabetic relatives than non-diabetics. The incidence was similar to that of relatives of individuals with diabetes of juvenile onset. Familial clustering of diabetes of juvenile onset is probably largely explained on the basis of HLA linkage (Renold *et al.*, 1978). None of the diabetics in this study had a family history of juvenile diabetes. It seems unreasonable to suggest that the association of FA and diabetes is a result of genetic linkage; if this were the case a higher incidence of diabetes would be expected in neurologically normal sibs.

SUMMARY

The clinical features of 115 patients from 90 families with Friedreich's ataxia are described. Onset of symptoms was before the age of 25 (mean 10.52) years in all the index cases. An analysis of early cases suggested that limb and truncal ataxia and absent tendon reflexes in the legs were the only consistent diagnostic criteria within five years of presentation. Dysarthria, signs of pyramidal tract dysfunction in the legs and loss of joint position and vibration sense are not necessarily present during the first five years of symptoms, but appear to develop eventually in all cases. Scoliosis and ECG evidence of cardiomyopathy were found in over two-thirds of the patients studied; pes cavus, distal amyotrophy, optic atrophy, nystagmus and deafness were all less frequent. The disorder was gradually progressive in all cases. The mean age of losing the ability to walk was 25 years; 95 per cent were chair-bound by the age of 44 years.

About 10 per cent of the patients had diabetes mellitus which was controlled by oral hypoglycæmic drugs in one quarter. Diabetes appeared to be associated with a higher incidence of optic atrophy and deafness. Diabetes also clustered within sibships; the risk of an individual with Friedreich's ataxia developing diabetes if an affected sib has it is over 40 per cent. Similarly, cardiomyopathy ran true within affected members of the same sibship, but there were instances of discordance which suggest that the development of the non-neurological features of Friedreich's ataxia may be controlled by modifying genes rather than heterogeneity of the main gene.

Segregation analysis and an increased consanguinity rate amongst parents of patients (5.55 per cent) confirmed that this disorder is of autosomal recessive inheritance. A study of 101 first degree relatives of the patients with Friedreich's ataxia failed to demonstrate any neurological or electrocardiographic abnormalities which could be ascribed to the heterozygous state.

ACKNOWLEGEMENTS

I wish to thank the following, who kindly allowed me to study their patients: Professors R. W. Gilliatt, J. Marshall, W. I. McDonald, J. Newsom-Davis and P. K. Thomas; Drs M. Baraitser, E. M. Brett, P. B. Croft, J. H. J. Durston, C. J. Earl, A. W. Ferguson, P. C. Gautier-Smith, J. Gawler, W. Gooddy, D. Harvey, P. K. P. Harvey, R. A. C. Hughes, J. A. Morgan-Hughes, R. Ross-Russell, G. D. Schott, G. Stern, J. Wilson and K. J. Zilkha; and Mr M. Edgar. Financial support from the Friedreich's Ataxia Group and the Medical Research Council is gratefully acknowledged. Mrs Lillian Nash from the Friedreich's Ataxia Group and Miss P. Goffron provided invaluable administrative assistance, and Professor C. O. Carter much helpful discussion.

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(*Received March 3, 1981*)

Brain (1981), **104**, 621–632

BRAIN INVOLVEMENT IN HEPATOSPLENIC SCHISTOSOMIASIS MANSONI

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INTRODUCTION

THE central nervous system may be involved by all three species of schistosoma infecting man. A number of authors have shown pathological brain lesions caused by *S. japonicum* (Greenfield and Pritchard, 1937; Chang, Smith, Riesenman and Alston, 1948; Kane and Most, 1948; Torres, 1965); *S. hæmatobium* (Gelfand, 1950; Alves, 1958; Gelfand, 1967; Chitiyo, 1972) and *S. mansoni* (Carrera, 1947; Raper, 1948; Valladares, 1953; Barros, Giannoni, Marigo and Frizzo, 1956; Alves, 1958; Raso *et al.*, 1964; Mattosinho-França, Malaragno Filho and Tenuto, 1965; Alemán, 1966; Queiroz, 1974; Pompeu and Sampaio de Lacerda, 1979). Spinal cord involvement by *S. hæmatobium* has been more commonly reported (Gelfand, 1950; Ghaly and El-Banhawy, 1973) and *S. mansoni* (Hinrichs, 1930; Espin, 1941; Gama and Marques Sá, 1945; Raper, 1948; Rocha and Roedel, 1952; Maciel, Coelho and Abath, 1954; Piquet-Carneiro, Alvariz and Serra, 1955; Abath and Barbosa, 1960; Marcial-Rojas and Fiol, 1963; Budzilovich, Most and Feigin, 1964; Herskowitz, 1972; Rosenbaum, Ishii, Tanowitz and Wittner, 1972; Ghaly and El-Banhawy, 1973; Perpétuo and Rodrigues, 1973; Queiroz, 1974; Queiroz, Nucci, Facure and Facure, 1979). Although a handful of previous papers deal with the various aspects of the disease the frequency of central nervous system involvement by schistosoma has still to be defined.

This fact may have two main explanations. First, in many cases there has been no pathological confirmation by autopsy and the diagnosis has been made from a history of exposure to the parasite; from the presence of eggs in fæces or rectal mucosa; from eosinophilia; from lack of a better explanation for the neurological symptoms and signs; and from a good response to specific treatment (Carroll, 1946; Kane and Most, 1948; Piganiol, Hervé and Pourpre, 1956; Zellmann, 1966; Blankfein and Chirico, 1965; Levy and Taube, 1969; Ruffino, Masson, Lange and Lesobre, 1970; Levy, Baldachin and Clain, 1975; *see*, too, review of the literature in Chang

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et al., 1948; Faust, 1948; Maciel *et al.*, 1954; Abath and Barbosa, 1960; Marcial-Rojas and Fiol, 1963; Blankfein and Chirico, 1965; Herskowitz, 1972; Perpétuo and Rodrigues, 1973).

Secondly, involvement of the central nervous system in schistosomiasis may be clinically silent and casually found at autopsy. The presence of eggs with no or scanty inflammatory reactions has been reported in brains and spinal cords of patients with schistosomiasis hæmatobium (Gelfand, 1950; Alves, 1958; Gelfand, 1967; Chitiyo, 1972) and schistosomiasis mansoni (Carrera, 1947; Valladares, 1953; Alves, 1958; Budzilovich *et al.*, 1964; Alemán, 1966; Queiroz, 1974).

This paper describes the frequency and patterns of brain involvement in hepatosplenic schistosomiasis mansoni which to our knowledge have not been previously reported.

MATERIAL AND METHODS

Forty-six cases of hepatosplenic schistosomiasis mansoni which came to autopsy at the Department of Pathology of the Federal University of Minas Gerais Medical School were taken at random for study. Most of these patients had died of gastrointestinal bleeding, congestive heart failure and infections. Eighteen of them also had cardiopulmonary schistosomiasis. The charts of 44 patients were reviewed in regard to clinical signs and evolution. In most cases histological sections of cerebral cortex, basal ganglia, cerebellar cortex, midbrain, pons and medulla were examined. Other cases also included sections of thalamus, hypothalamus and dentate nucleus. Paraffin-embedded sections were stained with hæmatoxylin and eosin.

RESULTS

Pathological evidence of brain involvement by *S. mansoni* was found in 12 cases (26 per cent). The pathological data are summarized in Table 1.

Of the affected patients 10 were males and 2 females, with ages ranging from 12 to 51 years. Nine patients were adolescents 12 to 18 years of age.

All but one patient had cardiopulmonary involvement. Most patients had either no neurological symptoms or clinical signs of terminal hepatic encephalopathy (Cases 9, 11 and 12). One patient had had a convulsive disorder (Case 6).

Gross examination of the brain was unrevealing but light microscopy disclosed scattered isolated ova in meninges and nervous tissue. More rarely ova were scattered in small clusters (figs. 1 and 2). The leptomeninges and cerebral cortex were most affected but changes were found in all structures examined. In 7 cases more than one area was affected and in one (Case 11) there was widespread cerebral involvement. In the majority of brains an inflammatory reaction, mainly of mononuclear cells or a granuloma, surrounded the schistosoma ova. In 2 cases, however, no inflammation could be observed. Localized vasculitis with fibrinoid necrosis of a small artery wall in the basis pontis was found in one case. In no case was the worm seen in histological sections.

TABLE 1. BRAIN INVOLVEMENT IN HEPATOSPLENIC SCHISTOSOMIASIS MANSONI

				Location								Histological features			
Case no.	*Sex*	*Age*	*CPS*	*CC*	*BG*	*CeC*	*Md*	*P*	*M*	*L*	*O*	*Granuloma*	*Infiltration around ova*	*No inflammation*	*Vasculitis*
1	M	12	+			+						+			
2	F	51	+	+									+		
3	M	18	+	+	+							+	+		
4	M	45	+							+	+		+		
5	M	12	+			+	+			+		+			
6	M	13	+			+				+		+	+	+	
7	M	12	+	+									+	+	
8	M	14	+					+				+			+
9	M	48	+	+				+		+	+		+		
10	M	17	—	+								+			
11	M	18	+	+	+		+	+	+	+	+	+	+		
12	F	12	+		+					+		+	+		

+ = present. — = absent. CPS = cardiopulmonary schistosomiasis. CC = cerebral cortex. BG = basal ganglia. CeC = cerebellar cortex. Md = midbrain. P = pons. M = medulla. L = leptomeninges. O = others.

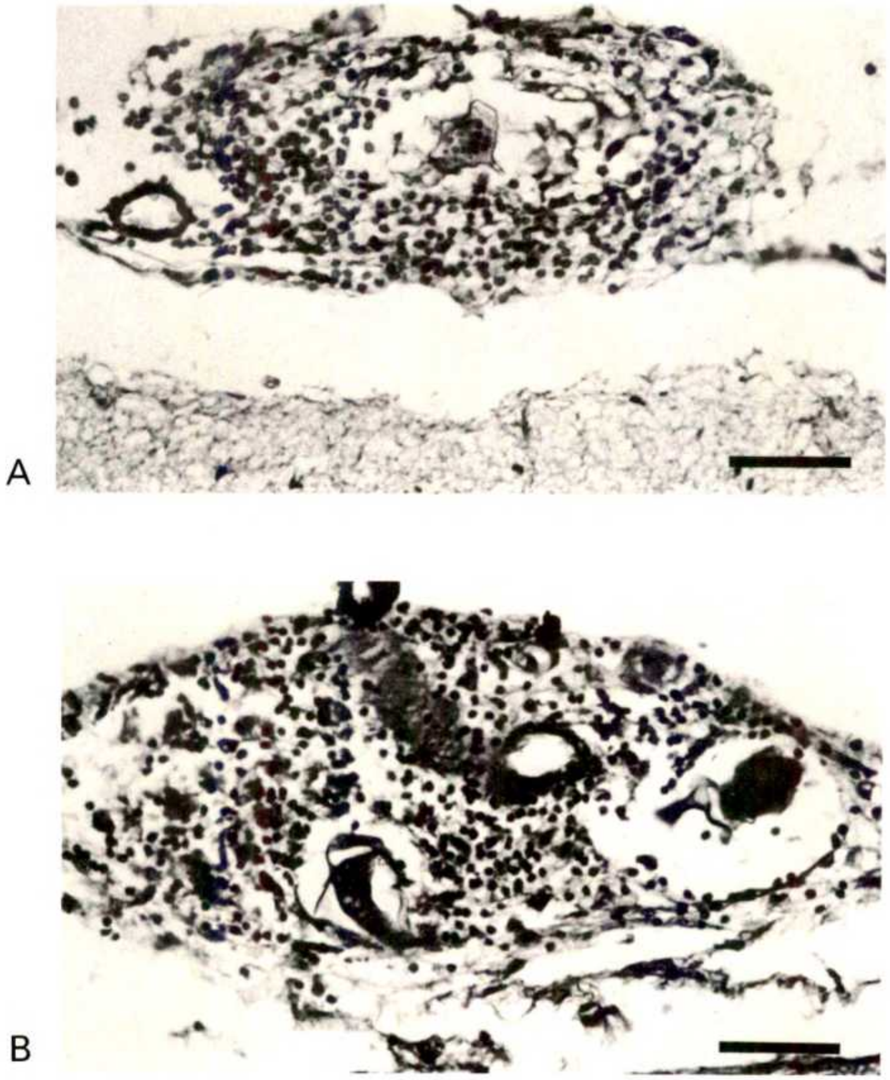
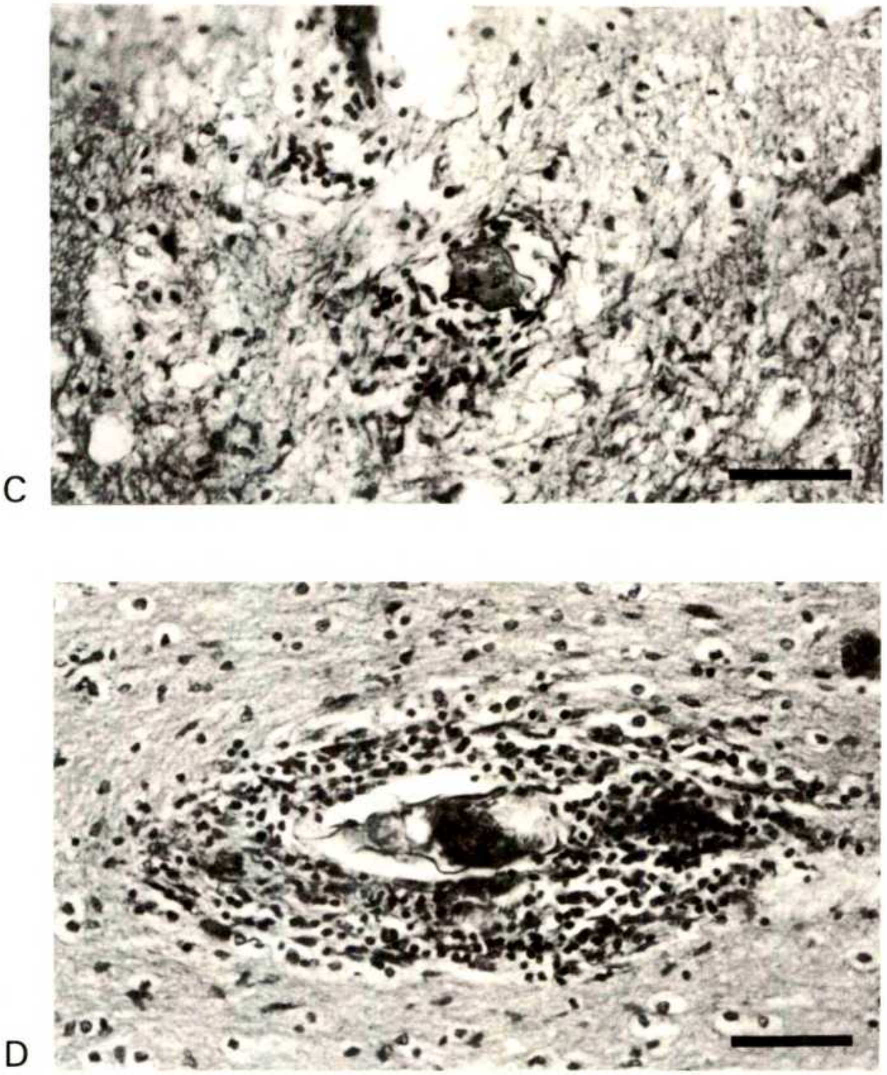


FIG. 1A. *Case 12.* Leptomeninges. Egg surrounded by lymphocytic infiltrate. H. and E. Bar = 50 μm. B, *Case 4.* Leptomeninges. Two eggs surrounded by lymphocytic infiltrate. H. and E. Bar = 50 μm. C, *Case 7.* Subcortical white matter (cerebral cortex). Egg surrounded by scanty lymphocytic infiltrate. H. and E. Bar = 50 μm. D, *Case 11.* Subcortical white matter (cerebral cortex). Egg surrounded by lymphocytic infiltrate. H. and E. Bar = 50 μm.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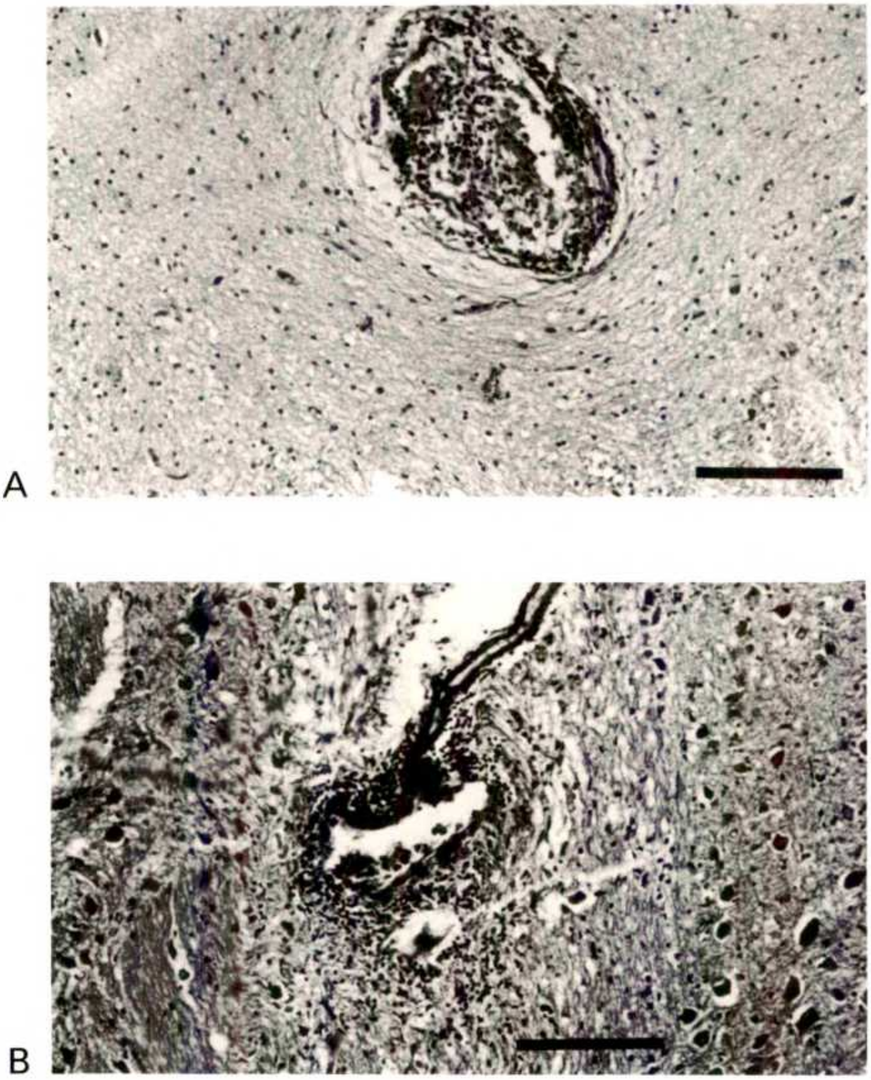
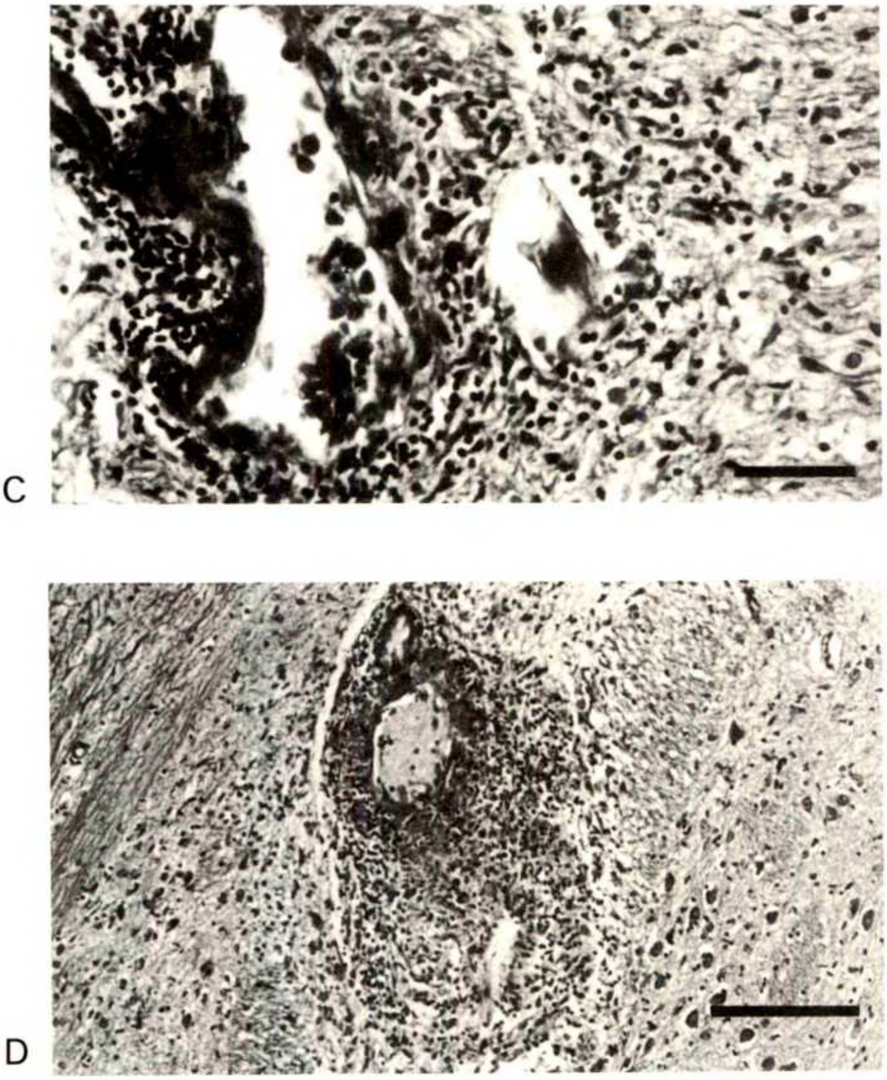


Fig. 2A. *Case 5*. Tegment of midbrain. Productive-phase granuloma. Ova were found elsewhere. H. and E. Bar = 150 μm. B, *Case 9*. Basis pontis. Paravascular egg surrounded by lymphocytic infiltrate. H. and E. Bar = 150 μm. C, *Case 9*. Higher magnification of fig. 2B. H. and E. Bar = 50 μm. D, *Case 8*. Basis pontis. Fibrinoid necrosis of small artery with predominantly mononuclear infiltrate. Eggs of *S. mansoni* were found elsewhere. H. and E. Bar = 150 μm.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DISCUSSION

Our findings suggest that the brain may be frequently affected in hepatosplenic schistosomiasis mansoni. As a matter of fact the majority of previously reported patients with brain schistosomiasis had hepatosplenic involvement (Barros *et al.*, 1956; Raso *et al.*, 1964; Mattosinho-França *et al.*, 1965; Alemán, 1966; Queiroz, 1974; Pompeu and Sampaio de Lacerda, 1979). It is worth noting that, as in our series, most patients also had cardiopulmonary involvement.

Although parasites' eggs have been found in almost all locations in the brain, the leptomeninges, cerebral and cerebellar cortex were most affected (Barros *et al.*, 1956; Raso *et al.*, 1964; Mattosinho-França *et al.*, 1965; Alemán, 1966; Queiroz, 1974; Pompeu and Sampaio de Lacerda, 1979). The microscopic picture is characterized by granulomas and lymphocytic infiltration around the ova (Barros *et al.*, 1956; Raso *et al.*, 1964; Mattosinho-França *et al.*, 1965; Queiroz, 1974; Pompeu and Sampaio de Lacerda, 1979). In two of our cases no inflammatory changes were seen in association with any eggs, whereas in other areas lymphocytic infiltration was prominent. Such a finding has also been reported in the literature (Valladares, 1953; Barros *et al.*, 1956; Raso *et al.*, 1964; Alemán, 1966). No adult worms were observed in the brain in our series, and have rarely been reported (Barros *et al.*, 1956). Vascular changes caused by *S. mansoni* in nervous tissue are uncommon. Cerebral and cerebellar hæmorrhage due to fibrinoid necrotic arteritis have been reported (Raso *et al.*, 1964; Mattosinho-França *et al.*, 1965; Pompeu and Sampaio de Lacerda, 1979). These vascular changes may cause parenchymal hæmorrhage but often this may not lead to clinical signs. Focal vasculitis was identified in two cases by Queiroz (1974) whereas in one of our cases (Case 8) fibrinoid necrosis of a small pontine artery wall was found, with no change in the surrounding nervous tissue. Immunological factors may play a major role in the striking variability of the morphological changes and clinical manifestations in human and experimental cerebral schistosomiasis (Abath and Barbosa, 1960; Jane, Warren and Van Den Noort, 1970; Ghaly and El-Banhawy, 1973).

Clinical signs other than those caused by cerebral hæmorrhage have rarely been described in association with cerebral schistosomiasis proved at autopsy. Coma (Raper, 1948), headache, vertigo and nausea (Barros *et al.*, 1956), seizure (Alves, 1958; Queiroz, 1974) have been reported. One of our patients (Case 6) had a convulsive disorder. Some of these signs have been ascribed to cardiac and respiratory involvement.

The parasite's path to the brain is still controversial. Embolization of eggs through the arterial system or by a retrograde venous route, or the laying of eggs during anomalous migration of worms through the brain (Faust, 1948; Queiroz, 1976) have been considered. The hypothesis of arterial embolization of eggs in the brain (Barros *et al.*, 1956; Raso *et al.*, 1964) supposes the presence of either pre-existing (von Hayek, 1970; Spencer, 1977) or disease-related (Barros *et al.*, 1956; Faria, 1956) pulmonary arteriovenous shunts. The arterial changes in pulmonary schistosomiasis which have previously been interpreted as arteriovenous fistulæ are now considered to be the result of organizing thrombi in the pulmonary circulation (Spencer, 1977). An alternate path for the arterial embolization of eggs to the brain would be related to the portal-pulmonary anastomoses through the azygos veins (Calabresi and Abelmann, 1957; Stein and Stein, 1961). This would be facilitated by the presence of portal hypertension. On the other hand, the arrival of eggs in the central nervous system through the venous circulation to the spinal cord has been suggested by some authors (Hinrichs, 1930; Gama and Marques Sá 1945). Faust (1948) suggested that the parasite may reach the central nervous system through anastomoses between veins of the brain and spinal cord and the portal system by way of the venous vertebral plexus of Batson (1940). The increased blood flow in the abnormal portal circulation would facilitate distribution by this route (Faust, 1948). This view is supported by the fact that most patients with brain schistosomiasis suffer from the hepatosplenic form of the disease. The laying of eggs in the brain after anomalous migration of the worms is supported by the finding of adult worms in leptomeningeal vessels (Barros *et al.*, 1956) and clusters of eggs in an area (Alemán, 1966). Although numerous eggs have been found within microscopic areas in the spinal cords of patients with schistosomiasis mansoni (Espin, 1941; Budzilovich *et al.*, 1964) and in the brains of patients with schistosomiasis hæmatobium (Gelfand, 1950; Chitiyo, 1972) and schistosomiasis japonica (Greenfield and Pritchard, 1937; Chang *et al.*, 1948; Torres, 1965), adult worms have rarely been reported (Raper, 1948; Chitiyo, 1972). Therefore, although the adult worm may reach the nervous system through the venous circulation, this migration is rather uncommon.

SUMMARY

The brains of 46 patients with hepatosplenic schistosomiasis mansoni were studied. Eggs of *Schistosoma mansoni* were found in 12 brains (26 per cent). The parasite location, brain reaction, clinical features and the possible paths by which the eggs of *S. mansoni* reach the nervous system are discussed. Our data and those of the literature suggest that brain involvement is common in hepatosplenic schistosomiasis mansoni.

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(*Received March 3, 1981*)

Brain (1981), **104**, 633–646

NOTICES OF RECENT PUBLICATIONS

Progress in Neurophysiology. Volume 8. **Spinal and Supraspinal Mechanisms of Voluntary Motor Control and Locomotion.** Edited by John E. Desmedt. 1980. Pp. 374. Basel: S. Karger. Price DM 165.00.

Professor Desmedt may be congratulated on gathering together so many well-written articles by experts in the field of movement control into one volume, and the publishers also for the quality of its production. There is no single, clearly emerging theme of research in this field at present and this is reflected in the somewhat contrived way in which the topics are divided into four groups. Under 'Sensory Input and Spinal Connectivities in Motor Control' we find articles on muscle spindles, gamma motoneurons, tendon organs and methods and results of studying certain spinal connections of the muscle afferents. The second group, entitled 'Segmental Circuits Involving Interneurones and Motoneurones', has three papers relating to the demonstration of various well-known spinal neural mechanisms in man, one on α–γ linkage and one on trigeminal motoneurons. In the third group headed 'Muscle Vibration and Motor Control in Man' all four papers relate to the activation of muscle spindles by vibration and the effects that can be observed. Finally, under 'Motor Control Mechanisms in Postural and Locomotory Activities' we have one presentation relating to the spinal pattern generator for locomotion and four considering how spindle and vestibular sensations help to regulate stepping and recovery from postural disturbance. There is evidently little justification for including 'Supraspinal' in the title of this book and the emphasis is really on the significance of muscle receptors and their spinal connection in movement control.

At the risk of over-simplification, a reviewer may divide papers into three categories according to their main emphasis. The first concentrates on methods, either presenting something quite new or adapting, modifying or checking a technique previously described. The second category uses established methods to gather some essentially factual data. The third approach is the one advancing novel concepts, the success of which can be measured not only by the extent to which they are justified now or in the future, but more particularly by the thought and experiment which they excite.

The paper most conspicuously dedicated to methods in this collection is the one by Kirkwood and Sears on the technique of spike-triggered averaging (often abbreviated to STA). The general technique of cross-correlation of nervous signals had been understood and used for some years before this particular version of it was introduced by Mendell and Henneman in 1968. These authors, and others since, have used it to very good effect as the most specific method available for examining synaptic connections, but there are special problems associated with it, and Kirkwood and Sears perform a useful service to would-be users by carefully reviewing the new considerations involved in interpretation of results. With STA one can look at the level of the minute effects produced by one presynaptic element on one target neurone. We now see the contribution of the individual members of the populations producing the classical large scale effects. One part of the price paid for this is the awful statistical odds that may be encountered by the experimenter trying to investigate pathways weaker or more diffuse than the projection of Ia afferents to motoneurons. Having isolated and characterized the firing of one presumed presynaptic element of interest it may be a very laborious and unrewarding task to penetrate a sufficient number of potential target neurons to get a useful estimate of the extent of the neural connectivity. However, once the basic method has been made available, many modifications may be devised and in the future one may expect it to be combined increasingly with micro-iontophoresis and with micro-anatomical techniques to study neuronal circuitry in detail previously unattainable.

The other contribution with a strong methodological content is by Pierrot-Deseilligny and Morin. This seeks to describe and to justify an ingenious and indirect means of estimating changes in the efficacy of Renshaw inhibition in man. A considerable intellectual effort is required to follow the description and the difficulty is aggravated by the choice of terminology and abbreviations, the tightly packed text, the complex illustrations and their solid blocks of small print legends. Expressed as simply as possible, the method consists in applying two stimuli to the posterior tibial nerve separated by 15 ms. The first stimulus is small and alone would cause a fractional H reflex (called H1). The second stimulus is large enough to cause a maximal M response. The H reflex efferent volley due to the first stimulus collides with the antidromic volley due to the second stimulus and so this does not reach the motoneurons fired by the first. These motoneurons are therefore able to be excited by the maximal Ia afferent volley due to the second stimulus, and give an H reflex called H′, which is equal to H1 or less by an amount which depends *inter alia* on the amount of recurrent inhibition set up by H1. Many indirect arguments are brought to indicate that other possible disturbances are insignificant or can be controlled and the author's skill and persistence are such that one must admit that they have a good case, though many neurophysiologists will feel uneasy at the need to get indirect support from so many sources. Happily, on some crucial points fresh supporting evidence has been obtained by Pierrot-Deseilligny and Hultborn in direct work in cats.

The main outcome of application of the method in man has been to indicate a reduction of Renshaw inhibition accompanying voluntary static and ramp contractions and an increase during unsupported standing. The reviewer must admit to some antipathy to the discussion of the significance of these results because of the facility with which support can be found for a number of quite different explanations of the significance of the Renshaw circuit. However, this work will undoubtedly attract much further interest and shows that designing human experiments capable of clear interpretation is a discipline every bit as demanding as animal experimentation.

For the second category of report referred to we have a number of papers, but to the reviewer none more interesting than that by Hultborn and Wigström. These authors show that in decerebrate cats a brief train of afferent impulses in Ia fibres, generated electrically or by vibration, can set off a contraction of triceps suræ which persists long after the end of the afferent input. To some degree the phenomenon shows the properties of a neural integrator, since the strength of contraction builds up linearly in proportion to the duration of the input train. A variety of experiments show the response not to depend on peripheral loops through say γ activity or tendon organ feedback, but indicate instead that it probably depends on spinal circuits of inter-neurons receiving excitation from spindle afferents and sending excitatory collaterals to the motoneurons. This work deserves to be taken very seriously since it indicates the existence of an excitatory multisynaptic pathway from Ia afferents to motoneurons which could be the basis for the 'tonic vibration reflex' (TVR) and functional stretch reflex (FSR) so much studied in man. The long latency of Hultborn and Wigström's effect and its dependence on spinal circuits must be taken into account when trying to interpret the TVR, FSR and so-called long-loop responses. One wonders also whether this is a mechanism of the kind sought for in the pathway of the vestibulo-ocular reflex. In this situation it has long been known that the signal generated at the vestibular nuclei by head turning is a frequency proportional to angular velocity. At the oculo-motor nuclei firing frequency is closely proportional to angular displacement, and consequently a neural integrator should exist between the two. Another possible speculation is whether an integrating mechanism at segmental level might not be a very efficient medium for descending control of certain movements. In many cases the nature of a motor task implies that information regarding the proper direction and speed of a particular movement is likely to be available to the parts of the nervous system inhibiting the movement, but its exact displacement required cannot be precisely predicted. If the descending motor drive were therefore in the form of a train of impulses at a frequency appropriate to the desired speed of movement then the 'integrator' could convert this to a smoothly increasing discharge of moto-neurons causing a smoothly increasing displacement. This could then be stopped by an appropriate sensory cue, for example, from cutaneous receptors excited by the limb touching the target. The cutaneous afferent volley could exert its stopping action at the spinal integrator or through ascending pathways to the motor cortex.

New data continue to be produced by the elegant techniques for recording excitatory afferent activity in man and animals. Two papers on this topic appear in this collection. One, by Prochazka describes spindle Ia discharge from hindlimb muscles in cats during walking and landing from a fall. The other, by D. Burke, Hagbarth, Lōfstedt and Wallin, examines spindle behaviour in man during vibration. The former work has yielded a good body of data on the behaviour of well-characterized Ia afferents in a wide range of natural movements. The general impression is of receptors responding most clearly to passive muscle lengthening with variable sensitivity. As in the case of similar data from jaw movements, there is no sign of spindle discharge leading active muscle shortening as would be required by Merton's length follow-up servo hypothesis. The variable sensitivity of the spindles indicates fluctuating fusimotor discharge, but unfortunately, the complexities of spindle response in relation to length change combined with changing static and dynamic fusimotor firing make it impossible to arrive at a clear statement regarding the discharge patterns of the two divisions of the specific fusimotor system relative to the α-motor. Certainly if α–γ co-activation can be said to occur, it is variable and sometimes weak or absent. One is increasingly caused to question the usefulness of the concept of α–γ co-activation. Its chief support comes from human work in which slow rates of muscle shortening allow quite small increases of fusimotor discharge to show themselves in the spindle afferent firing. What is particularly unfortunate is that observation indicating some degree of parallel action in α and fusimotor systems in a restricted range of movements in man has been taken by many to confirm this form of activity as an essential and general principle. Many times in this present collection of articles 'α–γ co-activation' is quoted to indicate what is likely to be happening during contraction of a variety of muscles in man and animals in many different situations, even though there is abundant evidence for the possibility of independent activation of α and static and dynamic fusimotor neurons. The history of this subject shows that workers like to identify a single principle, such as 'length follow-up servo', 'stiffness control' or 'α–γ co-activation', and then try to make all observations fit into it. Eventually when the evidence indicates too many exceptions, that principle falls out of fashion and we take up with another. It might be more profitable to recognize that the elaborate provisions which exist for regulation of spindle properties open up a wide variety of possible strategies for control. No one principle is likely to be sufficient to explain movement control in higher animals. Instead, we must think carefully about what might be good strategies for control in each different type of movement and then see whether experimental observation indicates which is actually employed.

A most valuable and lucid review of the various theories of fusimotor utilization is included in the paper by Matthews on 'Developing Views of the Muscle Spindle'. Much of this is quotable and the following lines may well be often repeated in the future when trying to explain the relative functions of static and dynamic fusimotor fibres: 'The static fibres inherited the role of being the servo input, if such a servo exists. A new role was required for the dynamic fibres since, especially during muscle shortening, they had too weak a direct excitatory effect on the afferent discharge to be able to reflexly drive the main muscle. Their function was then naturally seen as the regulation of the sensitivity of the primary ending to dynamic stimuli . . . '

The third category of paper referred to at the beginning of this review is well represented by those by Binder and Stuart and by Miller and Scott. The former authors advance the thesis that two types of movement can be distinguished. Stereotyped, repetitive movements such as in respiration and locomotion are contrasted with so-called 'Vernier' movements in which not more than 5 to 10 per cent of maximum force is developed. It is proposed that in the former type the whole ensemble of afferent input is brought to bear on all the motoneurons whereas in 'Vernier' movements the feedback may be very localized, with afferent activity arising in one very small part of the muscle projecting rather specifically to motor neurons of muscle units in that part. A cornerstone of this idea is that the anatomy of muscles provides for what is called 'sensory partitioning'; that is, that information about very precisely localized disturbance of force or length within a muscle is preserved in its passage to and through the motor nuclei and back to the muscle. Space does not permit a proper assessment of the detailed new and old evidence which is quoted in support of these ideas, but to read this article is to be constantly challenged to think anew about the complexities of segmental feedback control of muscle.

Miller and Scott have developed a model to suggest how the well-known elements of the spinal cord may be acting together to contribute a spinal locomotory rhythm generator. The beauty of this model is its economy in using (in its simplest form) only motoneurons, Ia inhibitory interneurons and Renshaw cells and their established connections. Activation of the generator requires only that there should be tonic descending excitation directed to the motoneurons and Ia interneurons. It also allows for interaction of the fusimotor system and muscle afferent influences.

The generalizations in Miller and Scott's article will certainly prompt many workers to try new experiments and this alone would give it an important place in the subject. There is even the possibility that their ideas are substantially correct, in which case they will turn out to have assembled many of the isolated jigsaw puzzle pieces of spinal reflexes into one particular meaningful picture.

Professor Desmedt has provided us with what would easily be taken for the proceedings of a Symposium on motor control. This is excellent in many ways, but it would have been most interesting to have heard the authors and others discuss the papers. As it is the reader must exercise all his own critical facilities. The effort will be found well worthwhile.

A. TAYLOR

The Extrapyramidal System and its Disorders (VIth International Syposium on Parkinson's disease). Advances in Neurology, Volume 24. Edited by L. J. Poirier, T. L. Sourkes and P. J. Bedard. 1979. Pp. 552. New York: Raven Press. Price $66.64.

The Sixth International Symposium on Parkinson's disease held in Quebec in 1978 must have been encouraging for neurochemists and pharmacologists who were able to report very rapid and interesting advances in their subject, but for those whose interest lies in treating patients with the disease, and for those who wish to understand the actual functions of the basal ganglia, it must have been rather depressing. Despite the title of the book it is not about the extrapyramidal system as a whole, but about the basal ganglia alone, and in particular about Parkinson's disease. We still lack a comprehensive account of the role of the basal ganglia in assisting movement; and despite advances in our understanding of their pharmacology Parkinson's disease remains incurable and relentless.

Nevertheless, this is one of the more useful volumes to have come the way of students of the motor systems for some time; the articles are short and concise and they cover the whole spectrum of disciplines which bear on the vexatious subject of the basal ganglia. As is unfortunately common with conference reports of this sort the book lacks real coherence or any attempt to draw together the various lines of evidence to offer a view of how the basal ganglia may function in health and disease. Nevertheless with imagination it is possible to see that a cloudy picture of what the basal ganglia do is beginning to emerge, even though nowhere is it explicitly articulated in the studies presented. Where textbooks of neurology or neurophysiology tend to conclude rather lamely that the functions of the basal ganglia still defy comprehension, by bringing together neuroanatomy, electrophysiology, pharmacology, neurochemistry, behaviour and neurology this volume makes a useful contribution to the emergence of a consensus.

This process will have been helped by the way in which contemporary thought about motor systems is changing. There has recently been a distinct shift away from preoccupation with reflexes and negative feedback control systems towards renewed appreciation of the importance to movement control of innate mechanisms for generating sequences of motor commands internally that do not have to rely at all on sensory feedback. In fact movements normally require both sorts of control: internally generated programmes to initiate and provide a basic pattern, and feedback to ensure accurate execution in relation to external conditions. Whatever innate mechanisms are responsible for generating prototype movement 'scores' they must play a major part in both involuntary and voluntary action. There are now compelling reasons for supposing that the chief function of the basal ganglia is to provide such self-generated blueprints for movement.

Much evidence for this view is to be found in *Advances in Neurology*, Volume 24. As one of the main reasons for studying the basal ganglia at all is in order to understand the movement disorders which follow their damage by disease, it is fitting to begin a review of the evidence contained in this volume that the basal ganglia contain skeletal programmes for movement by considering the consequences of their malfunction.

The diagnostic triad by which disease of the basal ganglia is recognized clinically consists of dyskinesia, involuntary movement and dystonia. All these symptoms in fact suggest what the basic functions of the basal ganglia are, though they are not often conceptualized in this way. Dyskinesia may be seen to represent deletion or disordered emission of internal movement formulæ; involuntary movements represent the release of crude motor programmes at inappropriate times; whilst disordered muscle tone may be viewed as injudicious choice of postural set for prevailing circumstances.

The sixth Symposium was not much concerned with such basic manifestations of basal ganglia disease; but was most exercised by the dyskinesias which accompany long-term L-dopa and neuroleptic therapy. These also reveal much about the normal behaviour of the basal ganglia. The movement disorders which occur in up to two-thirds of patients with Parkinson's disease when they are treated with L-dopa, are unlike those of the disease itself, being choreoathetoid, ballic or dystonic. For reasons that are not yet entirely understood the onward progression of the disease, in some cases hastened it is feared by the treatment itself, is probably associated with structural changes in membrane receptors, which cause them to become hyper- or desensitized. Such changes result in the release of 'choreo-athetoid programmes' at inappropriate times, thus revealing their location in the basal ganglia and something about how they are normally controlled.

Physiological studies in animals and man lend further support to these speculations. Parkinsonian patients rely much more than normal subjects upon visual feedback to help them to make movements. When blindfolded they are unable to maintain a constant limb position or to move precisely between targets presented to them beforehand. This is primarily because they are unable to form schemata—they cannot preprogramme movements before they take place or predict the movement of a sinusoidally moving target when it is temporarily blanked out; normal subjects can do this without any problems. Thus it appears that parkinsonian patients are unable to generate internal programmes for movement so readily; and rely much more on help from peripheral feedback (perhaps using their intact cerebella). The integrity of proprioceptive feedback systems was emphasized by the studies of Evarts *et al.* who demonstrated that the phase of parkinsonian tremor can easily be reset by appropriately timed stretch of wrist muscles. Tremor can thus be triggered by such stretches, but its frequency, presumably centrally programmed, is not much altered.

In phenothiazine-intoxicated monkeys, as in parkinsonian humans, a long latency component of the stretch reflex, which is thought to be partially mediated by the sensorimotor cortex, is enhanced as compared with normal subjects, although the monosynaptic spinal stretch reflex is unchanged. This again illustrates how sensory feedback is unimpaired in basal ganglia disease. To emphasize the increased amplitude of the transcortical stretch reflex may be rather misleading however. It is likely that the stretch reflexes have comparatively little direct mechanical effect in effecting load compensation. For example, they are probably more important in 'setting up' spinal cord parameters to ensure a standardized and linear background level of muscle stiffness upon which more powerful descending systems can then be brought to bear. Hence the augmented transcortical stretch reflex observed in parkinsonians is probably merely another way of looking at parkinsonian rigidity, rather than an indication of its cause.

A role for the basal ganglia in generating central automatisms is further supported by results obtained from recordings in trained monkeys. Powerful discharge of neurons in the main output regions of the basal ganglia, the globus pallidus and pars reticulata of the substantia nigra, precede specific types of movement of the limbs or trunk. Such neurons are probably somatotopically organized within these nuclei. They are hadly affected by proprioceptive, cutaneous, visual or auditory inputs. Such lack of sensitivity is to be expected since there are so few direct inputs from sensory systems to the basal ganglia. Output neurons therefore discharge before movement but not in response to sensory feedback; which is exactly what one would predict of neurons contributing to the internal programming of movements. However, neurons in the caudate nucleus and pars compacta of the substantia nigra which receive from each other, from the intralaminar thalamus and from the cerebral cortex are not so clearly related to movement, but instead appear to be cued by complex sensory stimuli which have behavioural relevance to the animal. It is possible that these are the neurons which control the triggering of movement programmes stored in globus pallidus and pars reticulata.

6-hydroxydopamine lesions allegedly restricted to the pars compacta of the substantia nigra have provided the most popular means for trying to relate the pharmacology of the basal ganglia to their role in motor control—in the 'rotating rat' model of Parkinson's disease. A timely contribution is therefore that of Butcher who shows that doses of 6-hydroxypamine greater than 4 μg spread beyond the pars compacta and affect the mesolimbic dopamine system as well, so that behavioural effects of such lesions may well be the result of damage to the limbic system rather than to the basal ganglia. Nevertheless animals in which destruction is confined to the dopaminergic cells of pars compacta exhibit decreased locomotor activity, supporting the idea that the substantia nigra normally is involved in generating locomotor programmes.

The major part of the symposium was naturally given over to the neurochemistry and pharmacology of the basal ganglia, as it is in this area that major progress has occurred. However, although a great deal has been learned about the details of the dopaminergic system, about its regulation and a certain amount about interactions with other transmitters, unfortunately there is virtually no attempt in this volume to link pharmacology with physiology to illuminate function.

A variety of new pharmacological ideas have emerged recently as a result of studying the basal ganglia. Dendrites as well as axon terminals have been shown to release dopamine. It is now clear that there are at least two different types of dopamine receptor probably having different membrane effects and often located at unconventional sites; furthermore these receptors may experience long-term alterations in their sensitivity under a variety of conditions. The problem of drug-induced dyskinesias exemplifies many of these new concepts. Choreoathetoid 'mid-dose' involuntary movements in parkinsonians are probably the result of postsynaptic DA receptors developing hypersensitivity. This process may either be a consequence of partial denervation caused by the disease or of long-term suppression of striate neurons caused by excessive dopamine treatment inhibiting them. It seems that excitation or inhibition may follow dopamine release depending upon whether adenyl cyclase linked or spiroperidol binding receptors are stimulated. Another complication is that these receptors may be located either postsynaptically, or presynaptically to terminals releasing other transmitters, particularly ACh and glutamate in the striatum and GABA in the substantia nigra. The consequences of interactions between dose-varying amounts of dopamine, and long-term changes in the balance of inhibitory and excitatory receptor activity are therefore, to say the least, unpredictable. However the mid-dose L-dopa dyskinesias can often be alleviated by reducing the dose of L-dopa without loss of clinical benefit. A simple interpretation of this observation is that excessive amounts of dopamine in the striatum are inhibitory overall, and thus remove the normal restraints excercized by the striatum on emission of programmes for archetypal choreoathetoid movements which are probably stored in the globus pallidus.

Release of more incapacitating dystonic or ballic movements occurs in about one-sixth of parkinsonian patients, usually the younger ones. These occur as plasma levels of L-dopa are rising or falling after or before a dose. They may be the result of a critical interaction between the two types of dopamine receptor which possess differing rates of development of hypersensitivity.

The two types of DA receptor may be associated with morphologically-distinct endings—the 'dotted' and 'diffuse' terminals of dopaminergic neurons. The dotted type has a lower overall amine turnover but higher concentrations of dopamine in local varicosities. These receptors are able to activate adenyl cyclase, whilst the commoner diffuse type bind spiroperidol, are found presynaptically on glutaminergic cortical afferents, cholinergic striatal interneurons and GABAergic terminals in the substantia nigra. They are specifically activated by bromocriptine. Although this agonist is not as powerful an antiparkinsonian agent as L-dopa, by affecting only presynaptic receptors it may avoid some of the hypersensitivity problems which accompany L-dopa therapy.

A crucial problem which has yet to be solved is the question of why both Parkinson's disease, leading to loss of dopamine, and L-dopa therapy, which leads to increased DA synthesis, may both cause receptor hypersensitivity. Two different mechanisms have been suggested. Denervation may cause proliferation of DA receptors—as if to be able to take better advantage of what dopamine is present—whilst excessive amounts of dopamine following treatment may overstimulate inhibitory DA receptors. This may either cause their regression directly, thus tipping the balance in favour of the excitatory ones, or by depressing the activity of striatal neurons favour the proliferation of excitatory DA receptors.

Another novelty is the concept of dendritic release of transmitters, especially dopamine. It has been suggested that release of dopamine from pars compacta cell dendrites serves an autoregulatory function, reducing the neuronal activity giving rise to it. This may be mediated either by inhibitory autoreceptors situated on dopaminergic dendrites themselves, or by excitatory DA receptors located presynaptically on GABA striato-nigral terminals. Their activation would cause the release of GABA which would inhibit compacta cell firing secondarily.

One might well ask why such a wealth of different transmitters and unusual synaptic mechanisms is crammed into the modest confines of the basal ganglia. The answer is surely to be found in the evolutionary significance of the basal ganglia. Ethologists have long favoured the idea that drive-related cues descending from higher centres are able to assemble simple motor sequences in a coherent order to create the complex patterns that constitute instinctive behaviour. Each component motor programme can be used to create a large number of different behaviours, as may be seen in single species performing different tasks and in the way related species carry out the same task, using different elemental movement programmes. It is therefore significant that the lower animals with the richest repertoire of instinctive behaviours have proportionally the largest basal ganglia. In the course of developing a large number of innate motor programmes over an evolutionary time scale, it is not surprising to find that many of the transmitter systems which were evolving simultaneously elsewhere were pressed into service within the basal ganglia.

J. F. STEIN

The Doctrine of the Nerves: Chapters in the History of Neurology. By J. D. Spillane. 1981. Pp. 467. Oxford University Press. Price £25.00.

Some historians insist that without history there is no science in medicine; 'technical expertise no more qualifies a man to practise medicine, to expand and readjust intellectually, than a metropolitan licence qualifies a taxi driver to negotiate the Gobi desert' (F. G. Crookshank). The historical approach, often adopted empirically by the individual, defines disease as an accident between body and cosmos and not as classifiable afflictions of individual organs. Nor can medicine be dissociated from social history. This is evident in advances arising from the study of war injuries and in peace by the impact of technical development as illustrated in the British Museum exhibition—Printing and the Mind of Man—in 1963. Many neurologists are attracted to the history of their subject for more personal reasons. Clinical detective work usually leads a surprising distance into the past. Some delight in the neurological discoveries in general literature and each has his own favourite; what was the nature of the temporary indistinct speech, irrational behaviour and drunken gait that affected Sir Edward Parry's exposed Arctic explorers in 1819? For others curiosity about the life, personality or work of a favourite individual (like Sir Charles Sherrington and Jean Fernel) starts an expedition into history. Many are martyrs to bibliophily, encouraged by A. N. L. Munby's view that 'to be thought a lunatic by one's fellow men is an insignificant price to pay for a lifetime's enjoyment' and by Sir William Osler who judged a man (favourably) by the proportion of stubs in his cheque book made out in the favour of booksellers. Whatever the individual reason, G. M. Trevelyan, in disclaiming a scientific approach to history, believes that 'the poetry of history lies in the miraculous fact that once on this familiar ground walked other men and women, as actual as we are today, thinking their own thoughts, swayed by their own passions but now all gone'. But this is also the essence of the historical approach to science.

As a result of neurologists' propensity for longevity neurological history is at present available by word of mouth through only three generations to the mid-nineteenth century and with the publication of eye-witness accounts of Vesalius' first public anatomical demonstrations (1540, published 1959) and Willis' *Oxford Lectures* (1661-1664, published 1980) to the sixteenth and seventeenth centuries. Few amateur historians can read early texts and some recent work (including many papers by Ramón y Cajal, for example) are not available in English translations. The advent of scientific journals has meant that the writings of individual authors may be widely dispersed and so the publication of collected papers (J. Hughlings Jackson 1925, 1932; Gordon Holmes 1979) is of the utmost value. Bibliographies make far from dry reading and the most complete list of 'classical original and standard works in the history of neurology' is that appended to Garrison's *History of Neurology* (1969). Apart from classical monographs on the history of aspects of neurology (including F. Fearing's *Reflex Action*, 1930, and E. G. T. Liddell's *The Discovery of Reflexes*, 1960) clinical monographs often contain definitive histories of their subject as, for example, Chapters 1-7, Volume 1, of *Aphasia and Kindred Disorders of Speech* (1926) by Sir Henry Head. The better known general histories offer biographical (W. Haymaker's *The Founders of Neurology*, 1953) pictorial (E. Clarke and K. Dewhurst's *Illustrated History of Brain Function*, 1972) anthological (E. Clarke and C. D. O'Malley's *The Brain and Spinal Cord*, 1968; A. Meyer's *Historical Aspects of Cerebral Anatomy*, 1971) or encyclopaedic (L. McHenry's *Garrison's History of Neurology*, 1969) approaches to neurology. Where should a historian begin? Dr. Charles Singer felt that no branch of medicine could have a history until it had moved from a demonic view of deviation from health due to entry of supernatural beings into the sufferer's body to a system based on observation. The Greeks therefore, although influenced by earlier Indian, Egyptian and Assyrian systems, head the evolutionary tree.

Dr Spillane starts with a chapter on Galen whose death in AD 200 brought an abrupt end to Greek medicine. Posterity has at times judged him harshly, claiming that he did no more than marry the substance of the Hippocratic corpus with Aristotle's philosophy and that the latter led to the teleological approach that has so exasperated some critics. But it was the theological conviction of a design following principles known to God (and Galen) that ensured the survival and influence of Galen's vast writings for the next 1400 years. The works of neurological interest are on 'On the usefulness of parts', not fully translated into English until 1968, and 'On anatomical procedures'. Galen's only manuscript of the latter was burned, twice, and rewritten. The single incomplete Western manuscript was first published in Greek (in 1525) then Latin (1531) and translated into English by Dr Singer in 1956. The missing part was unknown in the West, until the nineteenth century when an Arabic text was discovered in the Bodleian Library, was loosely translated into French in 1855, translated and published in German in 1906, translated from the original Arabic into English by W. H. L. Duckworth and published in 1962. These later books contain much on the brain, cranial and spinal nerves so that many neurological historians have only been able to judge Galen for themselves in the last few years. Dr Spillane illustrates by quotation the best of Galen (epilepsy, tremor, spinal cord and cervical root damage, the hand and muscles) the near misses (nature of the pulse, division of motor and sensory nerves and the optic chiasm) and the errors (recurrent laryngeal nerves and effluent ducts in the brain). He confesses to deep admiration for Galen's clinical abilities.

The Renaissance anatomist, Andreas Vesalius (1514–1564), the subject of Dr Spillane's second chapter, although much occupied in proving Galen wrong, founded his great work *De Humani Corporis Fabrica Libri Septem* (1543) on him. Harvey Cushing based his famous library on the works of Vesalius, yet his importance to neurology rests on two chapters (Book IV and Book VII) of De Fabrica, or more precisely on the illustrations since the text was not translated into English until 1952. The translator, Dr Singer, regarded this book as the foundation of modern medicine as a science and thought that no significant improvement has since been made on Vesalius' method, which was to dissect the (sometimes elaborately obtained) human body and look at it. All this by the age of 29. The book also established graphic illustration as an essential of biological research, for with the exception of Leonardo da Vinci, who did not publish his researches, no structural or physiological facts had previously been presented visually. As art the woodcuts (by Joannes Stephanus of Calcar) have rarely been bettered. Dr Spillane reproduces ten of the neurological woodcuts and points out unnamed but identifiable structures (basal ganglia and internal and external capsules) as well as commenting on several of Vesalius' anatomical and clinical descriptions (hydrocephalus, head injury and polyneuritis). He relates the tragic loss of a vellum copy of de Fabrica in Vesalius' birthplace, Louvain, in 1914 and the discovery in 1932 and subsequent destruction by Allied bombers of 230 original pearwood blocks. Vesalius' physiology deviates less from Galenic dogma than his anatomy but he did question the efflux of animal spirit down hollow nerves to all parts of the body subserving motor and sensory function because he could not see the holes. In the second edition of De Fabrica (1555) his account of the conversion of animal to vital spirit with the passage of blood across the interventricular septum of the heart is sceptical because he could not see the pits; a view possibly reinforced by having read a manuscript copy of the Catalonian Michael Servetus' *Restitutio Christianissimi* (1553). Servetus was burned at the stake in 1553 along with all but a few copies of the book but one survives in the Edinburgh University Library which was almost certainly owned and preserved by his persecutor—Calvin.

Thomas Willis (1621–1675) took a special interest in anatomical, pathological and clinical neurology, coined the term and wrote the first entire work on the subject. Dr Spillane takes the title of his own book from Willis and presents a careful defence of Lord Brain's (1962) view that Willis is 'the Harvey of the nervous system'. Dissention from such an opinion had started with Willis' contemporary Anthony Wood and was taken up by Sir Michael Foster (1901). Both accused Willis of mercenary motives and plagiarism whilst grudgingly conceding the value of his book *Cerebri Anatome*, beautifully illustrated by Sir Christopher Wren (1664). He was opposed or ignored by many others and Sir William Osler relegated all Willis' books to his bibliotheca secunda. The rehabilitation of Willis' reputation, starting in the late 19th century, gained momentum with Sir Charles Sherrington's gentle opinions (1940) and culminated in Sir Charles Symonds' vigorous defence (1955). Dr Spillane precedes his account of this debate with a more detailed account of Willis' views on the structure and function of the brain, the autonomic nervous system, endocrinology and clinical neurology than can be found elsewhere. The accusation against Willis was partly that his anotomical discoveries were really those of Richard Lower and that he failed to understand reflex function. But it is the opinion of F. Fearing and of Sir Charles Sherrington that, following Fernel and Descartes, he did. Dr Spillane pursues the development of reflex theory into the eighteenth century and although less concerned with individuals, two characters stand out. Each has been dubbed 'the Harvey of the nervous system', the Swiss Albrecht von Haller (1708–1777) by the German historian, J. H. Baas, and the Scot Robert Whytt (1714–1766) by J. F. Fulton. They were bitter rivals.

Haller's *Essay on Sensibility and Irritability* (1752) describes his theory of irritability, the tendency of a part to shorten on being touched by a foreign body due to an innate property of muscle (*vis insita*), and its distinction from *vis nervosa* which flowed down hollow nerves and might adventitiously stimulate muscles. Sensibility, the property of a part to transmit tactile impression to the brain, was localized to nerves. Supported by contemporary criticism Dr Spillane concludes that posterity has judged Haller generously since he did not appreciate or use the term reflex theory and dissociated irritability from the chain of events to which, renamed contractility, it rightfully belongs. Others see in Haller's *vis insita* the embodiment of the concept of reflex function and involuntary movement and judge that it is no criticism of Haller that a bogus school of therapeutics and a view of life was founded on his principles. Robert Whytt's discoveries include the first clinical description of a reflex (the pupil) the realization that involuntary movement is a response to stimulus independent of consciousness, the concept of tonic action, conditioned reflexes, the experimental demonstration of the role of spinal segments in reflex function and the original clinical description of tuberculous meningitis. John Unzer (1771) added the concept of afferent and efferent components in reflexes and George Prochaska (1784) reviewed other people's ideas well enough to be described (temporarily) as the founder of the doctrine of reflex function.

The question of priority in reflex theory arose again in the nineteenth century with a celebrated neurological dispute which Dr Spillane relates. Sir Charles Bell, supported by his brother-in-law, Alexander Shaw, claimed that his privately circulated essay (1811) and papers subsequently published in *Philosophical Transactions* demonstrated his recognition of the sensory and motor function of posterior and anterior roots and offered himself as 'the Harvey of the nervous system'. Time may have fogged his memory because as is well-known his early papers state the opposite and the subsequent correction post-dates F. Magendie's concise description of the truth (1822). Magendie had met Alexander Shaw's brother John in 1821 but allowed it to be known that he had received Bell's papers after his own publication and congratulated 'Mr Bell on so nearly discovering the function of the spinal roots'. The triangle is completed by Alexander Walker who decided that anterior roots were sensory and posterior motor (1809) but unlike Bell always maintained that this was correct (1839). Dr Spillane despairs of judging accusations of plagiarism against Marshall Hall's adoption of Whytt and Prochaska's teaching in his description of the reflex arc but Sir Charles Sherrington shifted from his belief that there was nothing original in Hall's writings to the view (1919) that his concept of reflex muscular tone in sphincter control was 'a first announcement'.

The works of physicians who described or illustrated the pathology of neurological disease in the 'exploratory first half of the nineteenth century' include J. Abercrombie's Textbook of Neuropathology (1828) and Sir Robert Carswell's Atlas (1838) with illustrations but no description of multiple sclerosis. Dr Spillane provides a valuable guide to J. Cruveilhier's randomly organized two-volume atlas (1829–1842). Emanuel Swedenborg's (1688–1772) holistic approach to localization of function in the nervous system is described and precedes a detailed account of two aspects of Franz Gall's (1758–1828) phrenology. P. Broca credited J. B. Bouillard with rescuing the organ of articulate language from the shipwreck of Gall's (and Spurzheim's) work and Broca contributed lateralization to their anterior localization of speech and distinction between written and spoken language, expression and comprehension and preserved lingual function in aphasia. Sir Henry Head (1926) also credits Gall with 'the origin of ideas we hold of the relationship between constituent parts of the nervous system'. In contrast Gall's localization of sexual function to the cerebellum leads Dr Spillane to a discussion of L. Rolando, F. Magendie and J. B. Bouillard's assignment of the regulation of posture to that organ. Sir David Ferrier's contribution to localization of function gives Dr Spillane an opportunity for some splendid neurological gossip. There is Professor Carpenter's account of his own and Ferrier's researches, monthly meetings at the West Riding Lunatic Asylum, reprimands at the Royal Society, the dispute between F. Goltz and Ferrier, Professor Charcot's astonished reaction to the hemiplegic monkey at the VIIth International Medical Congress and Ferrier's subsequent summons at Bow Street. Dr Spillane's account of this 'memorable decade' (1874–1884) and his excellent Hughlings Jackson lecture on the birth of American neurology are reprinted from earlier essays. Scattered throughout the last half of the book are sections on the impact of instruments on neurology (the ophthalmoscope and those used in the detection of electricity in the brain and nerves and its application) and the experimental neurologists, Claude Bernard and C. E. Brown-Séquard.

Great textbooks, documents of the history of neurology, appeared at the onset, middle and end of the nineteenth century. Dr Spillane has discovered John Cooke's *Treatise on Nervous Diseases* (1820–1823) for it is not well-known and the description of apoplexy justifies a place alongside John Cheyne's better-known book on that subject (1812). By implication Dr Spillane dismisses L. C. McHenry's view that M. Romberg's *Manual of the Nervous Diseases of Man* (1840–1846; English edition 1851) was the first systematic treatise on neurology but the book is original and, organized on the basis of disorders of sensation and motion, can claim to be the first comprehensive account of the symptoms of nervous disease. Many books published in the latter half of the nineteenth century were based on clinical lectures and Dr Spillane describes Sir Samual Wilks' lectures on diseases of the nervous system (1878) and those of Sir William Gull (collected edition 1894) Duchenne of Boulogne (1883 in English) and Robert Graves (1848) on paraplegia, muscle disease and neuritis, respectively.

These are well-known books but Dr Spillane closes with a description of the best-known book in neurology—Sir William Gowers' *Manual of Diseases of the Nervous System* (1886–1888). The author's reputation was established before publication and the book was bound to be widely read. Sir Norman Moore in his inaugural address to students at St Bartholomew's Hospital in 1893 advised them to make some acquaintance with the book and a recent reviewer in this journal chastised the younger generation of neurologists for being unfamiliar with it. It is doubtful whether there will be any readers of Dr Spillane's book who 'have not seen a copy' but his epitome of the work with reproductions of many of Gowers' line drawings will reveal new areas of interest to everyone.

Dr Spillane's book is a resounding success. His method is to demonstrate neurological history by edited quotations. He allows himself an opinion and enjoys it, particularly if controversial, although at times the temptation to be encyclopædic is not resisted and the underlying principle goes unsaid. Dr Spillane prefers people to principles, but in dealing with the nineteenth century it is no longer easy for him to identify the dominating individual as in earlier times; different aspects of neurology developed simultaneously and these are taken up, put aside and reappear in the attempt to round up stragglers. His selection of subjects cannot be criticized, for his aim is to select and offer what he 'would like the newcomer to hear . . . (the facts) that might liven his day' and his book is a treasure chest. It is profusely illustrated, using either the wide margins or full pages but one wishes that the publishers had allowed one of Sir Robert Carswell's hand-painted illustrations in colour. This is as much a book for the initiated as the curious newcomer which will be re-read for enjoyment and for its reference value. In this latter respect accuracy is important and, in spite of rapping Sir Michael Foster's knuckles for getting his dates wrong, Dr Spillane exposes himself to a few factual criticisms, the recognition of which will merely enhance the reader's self-satisfied enjoyment.

The great strength of this book is that it is written by a clinical neurologist with an infectious enthusiasm for his subject. From every page the image arises of Dr Spillane in Alexandria, in Padua, in Paris and at Gettysburg, a fly on the clinical wall, discussing cases with his predecessors. Who is the greatest individual in the history of neurology? In a final paragraph, rich in ecclesiastical metaphor, Dr Spillane casts his vote . . . for Thomas Willis and his Doctrine of the Nerves.

ALASTAIR COMPSTON

Low Level Lead Exposure. The Clinical Implications of Current Research. Edited by Herbert L. Needleman. 1980. Pp. 336. New York: Raven Press. Price $46.24.

The possiblity that exposure to lead is reducing the intelligence and permanently affecting the behaviour of our children is clearly an emotive issue. The subject is an obvious candidate for analysis by the media and attention of politically orientated environmentalists. It is interesting to review how the present climate of opinion has arisen. Much of the scene has been set in the USA but where appropriate, relevant studies have been carried out in the UK which have contributed usefully to our present knowledge.

Frank lead poisoning is a clear-cut clinical condition about which there can be little disagreement. In adults the well-known symptoms due to anaemia, colic and, more rarely, peripheral neuropathy occur. In children the condition manifests itself as encephalopathy. Partly because of increasing availability of chemical methods of estimating lead in blood and because of increasing awareness of the condition it became clear during the 1950s and 1960s that lead encephalopathy was common in children living in slum dwellings in eastern cities in the USA. Many hundreds of cases were diagnosed each year and at the beginning of this period the expected mortality was 25 per cent. With improved methods of treatment and earlier diagnosis the mortality fell. The source of lead was old lead-containing paints in the houses.

The question was then asked, what of the children living in such conditions who do not have frank encephalopathy? Surely pre-encephalopathic symptoms should be recognizable. And what degree of lead exposure can cause *any* symptoms?

Many studies during the past decade have been concerned with these questions. They have been of two types. Blood lead levels in groups of abnormal children, mentally deficient or hyperactive, have been compared with those in control groups. In several instances more lead has been found in the abnormal group (Moncrieff *et al.*, 1964; David, Clark and Voeller, 1972). Most of the authors have drawn only cautious conclusions from their studies, realizing the dangers of attributing the condition studied to lead poisoning. The second type has involved lead estimations in blood or in teeth in some recent studies as giving a better indication of previous long-term exposure. Then various behaviour and intelligence measures have been compared in groups of children with high and low lead levels. In some of the studies small differences have been found (Needleman *et al.*, 1979). The various studies have been reviewed and criticized recently by a DHSS working party, published as Lead and Health (1980). They stressed the difficulty of evaluating many of the studies; the difficulty in choice of controls, the problems of statistical analysis, and concluded that for blood levels over 80μg/dl symptoms occur, but below 35μg/dl there is no evidence at present to suggest deleterious effects. Between these levels the situation is unresolved, further work needs to be done and all attempts must be made to reduce exposure. Needless to say the report has been criticized in some quarters as underestimating the problem.

The commonest source of lead to children is still lead in paint. Emissions from factories concerned with lead have been much investigated and the effects on children living nearby. Here very much depends on the exact local conditions. There have been undoubted examples of unacceptable levels of pollution, but likewise studies near other lead works have demonstrated no harmful effects. Constant vigilance, monitoring and attempts to reduce pollution are important. Another focally important source of lead that has been recognized is domestic water pipes and tanks in areas where the water is plumbosolvent. Much attention had been given to this source by the Glasgow workers (Moore *et al.*, 1977).

The problems caused by these sources of lead are obvious and have been well documented. Where the scientific evidence is less clear-cut the emotional voices become stronger. This particularly applies to the importance as a pollutant of lead added to petrol. This lead contributes to the total lead in the environment and on general principles should be kept as low as possible. However there is no definite scientific data that lead from this source has been directly responsible for ill effects such as has occurred from exposure from the other sources discussed above.

Low Level Lead Exposure. The Clinical Implications of Current Research, edited by Herbert L. Needleman, consists of papers almost entirely concerned with the situation in the USA. They are the products of a symposium 'held under the auspices of the Office for Maternal and Child Health to communicate the newer data to clinicians who face daily management decisions and to public health officials who must devise effective regulations and preventative strategies'. There is bound to be a variability of standard in such a collection, but overall the scientific data is well presented with critical discussion of the results.

There is a very good introduction by R. K. Byers and an excellent historical review by Jane Linn Fu which show the evolution of events to the present state. The early clinical chapters are a little repetitive, but pull together much of the data that has been published elsewhere. There is a good chapter by Piomelli on biochemically detectable changes at very low levels of lead exposure. He laudably finishes 'To draw conclusions from this knowledge remains a challenge to the sensitivity of our society, to public health and preventative medicine' although perhaps with too great a tendency to argue earlier that detectable biochemical changes must be bad even when clinical effects cannot be detected. There is a too-long chapter by Cowan and Leviton concerned with epidemiological methods which is, however, admirably critical of many previous studies. Another good critical chapter by Mahaffey and Michaelson addresses the role of nutritional deficiencies in many of the animal studies of the effects of lead exposure on brain development, stressing the difficulties in many of them of attributing measured effects solely to lead intoxication.

In many ways the chapters which make the most entertaining reading are in the last section where battle lines concerning the public health issues in the USA are described and we can see the genesis of the emotions which surround the subject. Coers describes the conflicting opinions which were given to the Environmental Protection Agency based on the scientific evidence available. Schoenbrod, a lawyer, begins 'Little will happen, however, so long as scientists' active concern for human health gets squelched in a regulatory process geared to political ambition and industrial greed'. Emotive words. Other lawyers describe the consequences of the Lead-based Paint Poisoning Prevention Act of 1971 and the Massachusetts Childhood Lead-Poisoning Prevention Program. The habits of wicked landlords seeking to evade their responsibilities in de-leading apartments are described. Another lawyer, Bing,—'Data must be used aggressively to generate public support'. Scientific feet need to be kept firmly on the ground in the midst of such political furore.

In summary, this book gives an overall view of the present state. When I started to read it I had not really expected to get a clear answer to the question as to whether low-level lead exposure affected children's intelligence and behaviour and despite the many positive studies described I still do not think the association has been unequivocally proved. However, most of the scientists concerned seem aware of the criticisms levelled against them and there now seems a very real chance that further carefully designed studies over the next few years will clarify the situation. It is certainly no excuse for complacency, but it may be some comfort to review the achievements in the arts and sciences over the past twenty centuries and realize that only pre-Roman populations had concentrations of lead in their bones less than those in contemporary society (Waldron, 1979).

PAMELA M. LE QUESNE

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Receptors and Recognition (Series B Volume 9). **Neurotransmitter Receptors.** Part 1. Amino Acids, Peptides and Benzodiazepines. Edited by S. J. Enna and H. I. Yamamura. 1980. Pp. 212. London and New York: Chapman and Hall. Price £15.00.

This book contains five chapters well written by acknowledged experts. Each has summarized information relating to the physiological, biochemical, pharmacological and functional characteristics of neurotransmitter receptor sites.

It is now recognized that many different compounds act as neurotransmitters within the central nervous system. It is also known that released neurotransmitters interact with specific receptor molecules which may be located at both pre-synaptic and post-synaptic sites. Thus, the undecapeptide, substance P, appears to modulate dopamine and serotonin release by first acting on pre-synaptic receptors. In the post-synaptic region interaction with receptors is a key step in neurotransmission. As is pointed out in this book, development of receptor-ligand binding methods has greatly facilitated ways in which such receptor function can be studied. For example, the order of potency of physiologically characterized agonists and antagonists can be correlated with competitive efficiency at the binding site. In Chapter 4, Childers describes how opiate receptors were detected by biochemical techniques using binding of radioactive drugs to brain membranes. Endogenous opioid peptides (the enkephalins and pituitary endorphins) and later a group of brain-gut peptides (angiotensin, vasoactive intestinal peptide, etc.) were discovered.

In his review of the role of the excitatory amino acids and excitotoxins, Coyle concentrates on glutamate and aspartate. Enna and De France deal with the very topical work on GABA and glycine receptors and the concept of benzodiazepine binding. In Chapter 3, Hanley and Iversen argue convincingly that studies on substance P receptors are further advanced than those for most other putative neuropeptides (the subject of Burt's Chapter 5). The subject of catecholamine and cholinergic receptors will be dealt with in Part 2 of the present series.

Although this volume is intended to be an introduction to young neuroscientists, it is likely to be of particular value to the more experienced research worker.

A. N. DAVISON

Handbook of Clinical Neurology. Volume 41. **Diseases of Muscle.** Part 2. Edited by P. J. Vinken and G. W. Bruyn, in collaboration with S. P. Ringel. Associate editor, H. L. Klawans. 1980. Amsterdam: North-Holland Publishing Company. Price Dfl. 245.00.

As the editors observe in their foreword 'the clinical descriptions of the muscular dystrophies... have remained virtually unchanged' since the early accounts of the last century. The causes of many important diseases of muscle remain unknown and useful treatment is often unavailable. Volume 41 of the Handbook contains a series of chapters written by authors established as authorities in their different subjects, for example, Hudgson and Walton, Engel, Penn and Layzer. Some chapters appear overlong in relation to the topic served as the author explores every conceivable aspect of his subject, particularly when so many negative or agnostic reports are cited. Nevertheless, the reader wishing to cover the ground relating to any aspect of muscle disease will find a remarkable breadth of information and reference within these covers.

R. A. HENSON

The Prefrontal Cortex. The Anatomy and Neurophysiology of the Frontal Lobe. By Joaquim M. Fuster. 1980. Pp. 220. New York: Raven Press. Price $34.00.

Books on frontal lobe function which are other than conference proceedings are very rare. This one is especially welcome as Fuster has written a scholarly and fairly comprehensive review of the literature. He covers anatomical studies, lesion studies in animals, electrophysiological studies and studies of the effects of frontal lobe lesions in humans. Despite a density of references more typical of a review article, the book is fairly easy to read, being both well written and well argued.

The book has two rather disappointing aspects. The section on human neuropsychology is weaker than the other sections, with no attempt made to differentiate reports of clinical observations and experimental studies. Secondly, Fuster's theory of frontal lobe impairment as an inability to construct and utilize temporal Gestalts is vague and based on concepts which are out of date within psychology. However, these are relatively minor problems. The book is likely to remain a standard reference work for a considerable time.

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Printed in Great Britain
at the University Press, Oxford
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Printer to the University

ISSN 0006-8950

Acc. 27.9.82

Brain

A Journal of Neurology

Volume 104 Part IV December 1981

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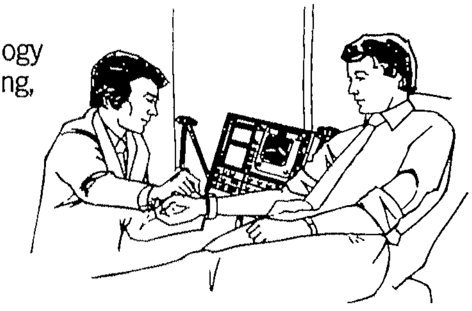

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Publication schedule and subscription information:

1982 – Vol. 2 (1 volume in 4 issues)
Subscription price: US $80.75/
Dfl. 202.00 including postage.
ISSN 0165-5728

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LOCOMOTOR CONTROL IN MACAQUE MONKEYS

by E. EIDELBERG, J. G. WALDEN *and* L. H. NGUYEN

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INTRODUCTION

IN two recent reviews Grillner (1975) and Orlovsky and Shik (1976) defined a model of the organization of the locomotor control system in vertebrates. It consists of two linked sets of elements: a supraspinal 'command' centre—or group of centres—and spinal step generator circuits for each limb. The command structures, located subcortically, modulate (that is, initiate, stop, slow down or accelerate) the actions of the spinal pattern generators. The latter contain the detailed programs for execution of the complex sequences of muscular contractions which underlie walking, running or swimming. The actions of these two basic control units may be modified by signals from other parts of the central nervous system, or by feedback from peripheral receptors. This model has a long history: Central (spinal) pattern generation was proposed by T. Graham Brown (1914) as the explanation for his finding that animals that had the spinal cord transected and the lumbosacral dorsal roots cut were capable of hindlimb stepping. Brown's experiments have been reproduced in several laboratories using cats or rabbits as the subjects, but certain electrical and pharmacological measures were required to elicit stepping soon after spinalization (Budakova, 1973; Forssberg and Grillner, 1973; Grillner and Zangger, 1979; Viala and Buser, 1969, 1971). In chronically spinal cats and dogs stimulation by certain postures, motion, electrical shocks, or exercise, was relied on to initiate or facilitate stepping (Eidelberg, Story, Meyer and Nystel, 1980; Forssberg, Grillner and Halbertsma, 1980; Freusberg, 1874; Grillner, 1973; Shurrager and Dykman, 1951).

As to the central command structures, Magendie (1845) showed that decerebrate rabbits are quite capable of locomotor activity. Graham Brown prepared a film, shown to the Physiological Society in 1941, where decerebrate (precollicular) cats were shown walking on a treadmill. There is a description of this film by Lundberg and Phillips (1973). In 1924 Laughton showed that cats, dogs and rabbits generated what he called 'coordinated progression' movements after transection of the neuraxis at levels as low as the midbrain; such activity was elicited by electrical stimulation of the caudal surface of the sectioned brain stem. Hinsey, Ranson and McNattin (1930) and Waller (1940) extended Laughton's observations by showing that localized electrical stimulation in the vicinity of the subthalamic nuclei and other brain-stem areas elicited co-ordinated four-legged 'locomotor' movements. Grossman (1958) showed that concurrent stimulation of the centro-median nuclei of the thalamus inhibited this motor behaviour. Since then several investigators have refined these observations, and have described a series of subthalamic, mesencephalic and pontine 'locomotor regions' (Grillner and Shik, 1973; Mori *et al.*, 1977, 1978; Orlovsky, 1969; Shik, Severin and Orlovsky, 1967). We note that 'locomotor regions' are physiological and not anatomical concepts, in that the movements observed could be due to activation of cell bodies near the electrodes or of axons originating elsewhere and traversing the stimulus site.

There is no evidence for a similar system of locomotor control in primates, including man. There are no published accounts of clear-cut 'spinal stepping' in monkeys or man after verified complete cord transection. In the classical paper by Holmes (1915), he mentioned alternating stepping-like activity of the legs of a few patients with missile injuries of the cord, but the two who were later studied at autopsy proved to have incompletely transecting lesions, with sparing of the ventral sectors of the white matter. The same applies to Riddoch's (1917) report. Stepping-like behaviour was found in a patient with a complete transection of the cord in Kuhn's series of cases (1950). This activity was triggered by elicitation of flexor and crossed extensor reflexes and was sustained only briefly. We are unaware of published tests of the existence of brain-stem locomotor regions in primates.

We sought to investigate these two questions, and added a third: which pathways in the monkey's spinal cord must be spared by an incomplete section if a monkey is to recover locomotor function? A previous series of experiments in cats yielded strong evidence that axons issuing from the vestibular, posterior pontine, and gigantocellular medullary reticular nuclei may be critically involved in the return of walking (Eidelberg, Story, Walden and Meyer, 1981), and so our search centred on these structures.

METHODS

We used 'cynomolgus' macaque monkeys (*M. fascicularis*) whose ages were estimated to be between 2 and 4 years, and whose weights ranged between 3.0 and 5.2 kg. To search for spinal stepping we carried out two kinds of experiments: in Group 1 we attempted to elicit this phenomenon immediately after spinal cord transection. In Group 2 we used chronic spinal preparations that were tested for hindlimb stepping for up to four months after cord transection. To identify the pathways responsible for the recovery of locomotor activity after *partial* spinal cord lesions (Group 3) we trained monkeys to walk on a moving treadmill belt, operated upon them, and re-tested them serially until stable performance was reached. We identified the spared descending pathways by histological study of the lesion sites and by retrograde labelling with horseradish peroxidase injected into the lumbosacral cord (Eidelberg *et al.*, 1980, 1981). The experiments on 'controlled locomotion' (Group 4) were carried out on monkeys decerebrated at the midthalamic level. Bursts of electrical stimuli were applied through exploring electrodes which were lowered step by step through the posterior diencephalon and midbrain, while the animals' feet were in contact with a moving treadmill belt. The presence of rhythmic alternating movements of the limbs induced by the stimulation was regarded as 'controlled locomotion'.

Group 1. Acute Spinal Stepping ($N = 8$)

The preparations used followed in general those described by Grillner and Zangger (1979). The animals were anæsthetized with sodium methohexital (Brevital (Lilly) i.v.), and decerebrated with a blade introduced vertically so as to section the hemispheres and diencephalon frontally at A10–A12 (Snider and Lee, 1961). A laminectomy (T6–T8) was carried out to transect the spinal cord and prepare the dorsal columns (caudal to the transection) for stimulation through a pair of platinum wire electrodes. Both popliteal spaces were exposed, the nerves to the triceps suræ and tibialis anterior muscles were cut, and their proximal ends were placed on pairs of recording electrodes. 'Fictitious locomotion' was defined as the presence of bursts of multiple action potentials in these muscle nerves, in an alternating pattern similar to that of stepping in intact animals (Perret, 1976). The animals were immobilized by gallamine (Flaxedil (American Cyanamid), 2–3 mg/kg/h) and ventilated with a pump. To elicit stepping we injected the animals first with nialamide (50 mg/kg). 30 min later L-dopa methyl ester (Sigma), 100 mg/kg was given intravenously and trains of electrical stimuli were applied to the dorsal columns (50 pulses/s, 0.5 ms, 3 mA) every 5 to 10 min for up to 2 h (Grillner and Zangger, 1979). To look for other actions of dopa on the spinal cord we prepared 2 additional monkeys in the same general manner, but recorded instead the flexor reflex bursts elicited in the nerves to the posterior biceps and tibialis anterior muscles by short trains of stimuli to the sural nerves (50 ms trains, 100 pulses/s, 0.2 ms duration). Andén, Jukes, Lundberg and Vyklicky (1966) have shown, in cats, that dopa reduces the initial flexor reflex but induces a late (200 ms latency) discharge in these nerves. Russell and Zajac (1979) have reported that the severe pressor responses induced by the nialamide-dopa combination could be avoided by pretreatment with a peripheral inhibitor of dopa decarboxylation (R04-4602, Roche). They showed also that fictitious locomotion was potentiated by adding 4-aminopyridine to the other drugs, presumably as a consequence of this drug's ability to enhance transmitter release at central synapses (Thesleff, 1980). Two monkeys were spinalized as before, and treated with the following drug sequence: R04-4602 10 mg/kg first, dopa methylester 50 mg/kg 30 min later and 4-aminopyridine 0.25 mg/kg 30 min afterwards, repeating the latter at 10-min intervals to a total dose of 1.0 mg/kg.

Group 2. Stepping by Chronic Spinal Monkeys ($N = 6$)

These animals were trained to walk on a treadmill at speeds up to 2.0 $m.s^{-1}$, for a food reward (fruit juice) delivered after 15 s of continuous walking. Later on they were anæsthetized (pentobarbital sodium, 35–40 mg/kg, i.v.) and the spinal cord was transected between T8 and T9, using a curved hook to verify the completeness of the cut. The animals received appropriate post-operative care (soft floor, exercise, penicillin for a week, and bladder expression twice daily). They were re-tested daily on the treadmill, with a sling support for the hindquarters adjusted so that the hip joints were maximally extended by the belt motion (*see* Eidelberg *et al.*, 1980). The re-testing period extended beyond the recovery of segmental reflexes below the transection, from six weeks to four months after operation. Each animal was injected in several separate occasions with clonidine (0.5 to 1.0 mg/kg), i.v.

At the end of the observation period each monkey was subjected, under general anæsthesia and *via* a laminectomy, to injection of 50 to 100 μl of a 15 per cent solution of horseradish peroxidase (HRP) into cord segments L7 to S1. Three days later, again under anæsthesia, they were perfused with fixative (glutaraldehyde 1.25 per cent, paraformaldehyde 1 per cent in phosphate-buffered saline at pH 7.4) through the left heart ventricle. The site of the cord transection was blocked and cut serially (paraffin) and the sections were stained with a variant of the Bodian method, to look for axons crossing the gap (now filled with connective tissue). None were found, and no HRP-labelled cells were found in the cervical cord, brain-stem or precentral cortex, confirming the completeness of the transection. The details of the methods used in this group are described in a previous report from this laboratory (Eidelberg *et al.*, 1980).

Group 3. Partial Spinal Cord Lesions ($N = 10$)

These monkeys were trained, operated on, and re-tested in the same manner as the animals in Group 2, but we attempted to spare certain sectors of the spinal cord. Retrograde labelling with HRP was used, in addition to histological study of the lesion sites, to identify the descending axons which escaped transection. Their cell bodies of origin in the brain-stem were identified and mapped by an x-y plotter coupled to the microscope stage, and later reconstructed on Oertel's (1969) stereotaxic atlas for the brain-stem of the macaque.

Group 4. Controlled Locomotion ($N = 4$)

The subjects were anæsthetized with methohexital while the preliminary operation was carried out, including arterial (carotid) and vein cannulation, tracheostomy and decerebration. The latter was done with the head in a stereotaxic frame; a spatula was driven vertically into the brain, sectioning the hemispheres and diencephalon in the frontal A10 plane; the cuts extended at least 15 mm lateral to the midline. After this the animal was placed above a variable-speed treadmill and suspended above it by the headholder and a clamp on a lumbar spinal process, so that all limbs rested upon the belt. A concentric pair of steel electrodes, (0.D. 250 μ) held in a stereotaxic carrier, was guided into the brain in 1 to 2 mm increments so that the posterior diencephalon and the midbrain were explored in a three-dimensional grid of stimulus sites. At every new position of the electrodes a train of stimuli was delivered after the treadmill was started up (0.5 $m.s^{-1}$). The search stimuli were 5-s trains, 50 pulses/s, 0.2 ms, 200 μA. When a 'positive' locus was discovered, a series of stimulus trains of decreasing intensity was used to define a 'threshold' (sometimes as low as 25 μA), while a moving camera recorded the motor consequences (Super 8, 54 frames/s).

At the end of the experiment several landmark positions were marked by passing DC current through the electrodes, and the animals were perfused with 10 per cent formalin for later histological (frozen serial sections at 50 μ) verification of the decerebration lesions and the electrode tracks. The method used in this experiment was taken from the description by Shik *et al.* (1967). The electrode positions where stimulation yielded stepping were reconstructed upon tracings from a standard atlas (Snider and Lee, 1961).

RESULTS

Group 1. Spinal Stepping, Acute Experiments

None of the monkeys in this group showed electrical signs of alternating discharges in hindlimb flexor and extensor muscle nerves resembling the pattern of locomotor activity ('fictitious locomotion'). It made no difference whether we used a nialamide-dopa sequence or a R04-4602-dopa-4-aminopyridine combination; the same held for stimulation of the dorsal columns as adjunctive means. In two other animals, not listed in Methods, we attempted to elicit hindlimb stepping soon after spinalization by supporting the animals above the treadmill, as in Group 4. These monkeys had been decerebrated and were treated with the R04-4602-dopa-4-aminopyridine combination. Their forelimbs were rather rigid and stepped almost every time the treadmill started moving. The hindlimbs were dragged backwards flaccidly by the belt, to maximal extension, without showing even traces of flexion (Grillner and Rossignol, 1978).

As described in Methods, we searched for the actions of the triple drug combination upon flexor reflexes and late flexor discharges described by Andén *et al.* (1966). There was a minor but definite decrease in the early flexor reflex responses, and a sharp increase in traffic of axon spikes past the electrodes, but no late discharges were detected.

Group 2. Spinal Stepping, Chronic Experiments

These were carried out upon monkeys trained to walk on a treadmill prior to transection of spinal cord. After transection they displayed the classical picture of 'spinal shock' described in detail by many others before (Liu, Chambers and McCouch, 1966; McCouch, Liu and Chambers, 1966; Sherrington, 1906, 1910). As described by these authors, the animals gradually recovered over a period of three to four weeks to the point that the hindlimb muscles showed good tonus, the knee, ankle and adductor tendon reflexes were present, and usually brisker than before the transection, the bladder was automatic, etc. The animals were kept and re-tested serially at least for six weeks after operation (one was kept for four months). None showed stepping motions on the treadmill, even when the hindquarters were supported externally so as to allow maximal hip extension and thus facilitate the onset of the flexor (swing) phase of the step cycle (Grillner and Rossignol, 1978). Clonidine, at the same doses used to elicit stepping in acute spinal cats (Forssberg and Grillner, 1973), failed to do so in these preparations. Skin stimulation (pinching of the thighs or base of the tail), which is often effective in eliciting stepping sequences in chronic spinal cats (Eidelberg *et al.*, 1980), was ineffective in these monkeys.

Group 3. Partial Spinal Cord Lesions

Most of the monkeys in this group had lesions placed so as to spare the ventral quadrants on one or both sides, because of previous experience with cats (Eidelberg *et al.*, 1981) and some pilot experiments with untrained monkeys. We classified them by outcome, in three groups: Group *a* (2 monkeys) were incapable of support by the hindlimbs and showed no stepping movements with them. Group *b* (2 monkeys) exhibited some weak and irregular stepping-like movements, without support or propulsion by the hindlimbs. All the monkeys in Group *c* recovered eventually the ability to support their hindquarters and to step and propel with the hindlimbs. The survival of monkey No. 13 (Group *b*) may have been too brief (one month) for maximal recovery of performance. Of the animals in Group *c*, No. 1 walked unsupported at speeds up to 1.5 $m.s^{-1}$, reaching this level almost two months after operation. Monkey No. 6 began to step twenty-one days after operation, could do so unsupported after thirty days, and reached 1.5 $m.s^{-1}$ at thirty-six days after surgery. Monkey No. 14 stepped first with the left hindlimb (same side as the spared ventral quadrant), later with both. No. 18 began stepping, unsupported, one week

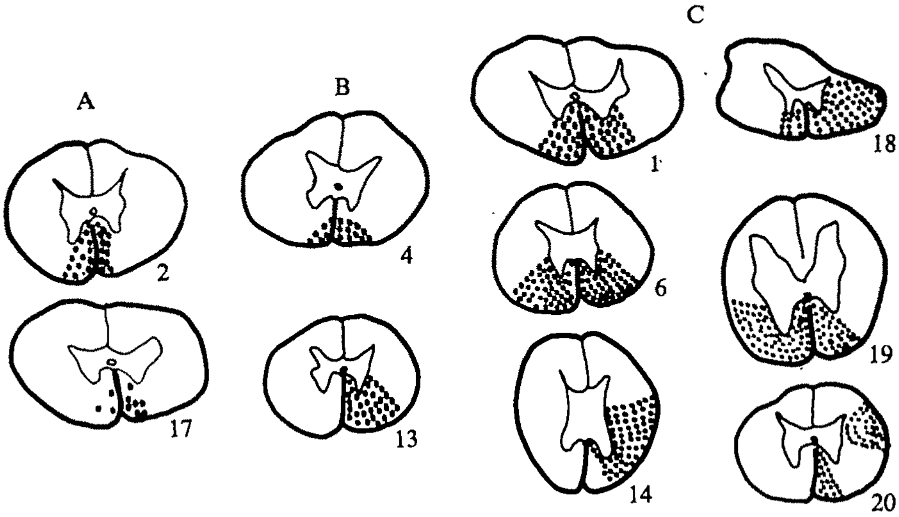

FIG. 1. Localization of the spared white matter in the monkeys of Group 3 (*see text*). Reconstructions from serial transverse sections of the spinal cord stained for axis cylinders. Dotted areas indicate the presence of substantial numbers of spared axons.

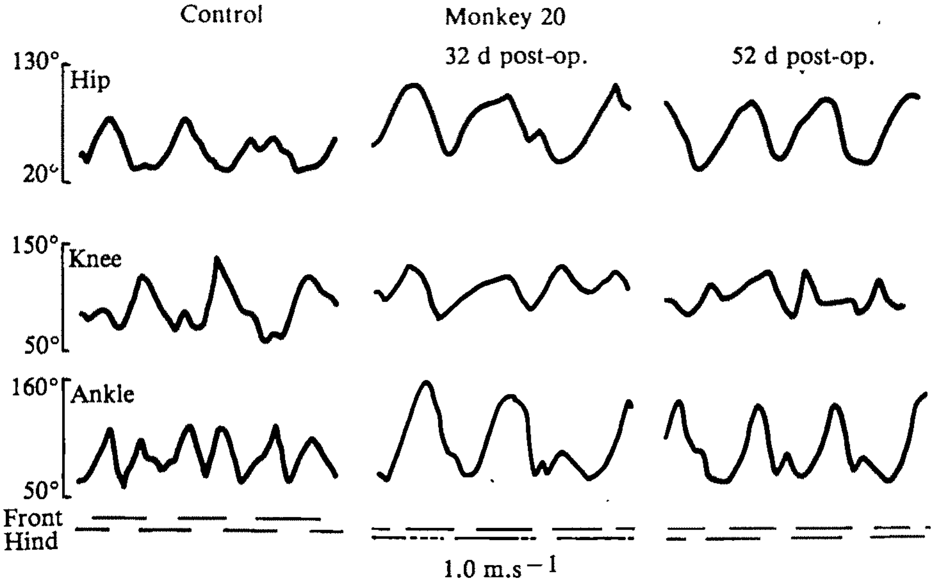

FIG. 2. Joint angle trajectories (3–4 step cycles/sample) of a hindlimb before and after partial cord section (*see* fig. 1 for localization). Extension upwards, flexion down. The footfall markers below indicate the timing of floor contact by the ipsilateral forelimb and the contralateral hindlimb (solid lines). Dashed lines signal limb flexion ('swing phase') without lift-off.

after surgery. The right hindlimb (hemisected side) did not step at first, but began doing so on the twenty-first day. No. 19 supported and stepped vigorously with both hindlimbs by the seventh day after surgery. No. 20 began to walk unsupported one month after surgery and kept improving for another month, at which time he could walk at up to 1.0 m.s^{-1}. (*See* figs. 2 and 3 for representative recordings from this animal.)

The extent of axonal sparing in each subject is described in fig. 1. Because of the deformations introduced by scar tissue and cyst formation it can be considered only as a rough approximation. The distribution of retrogradely labelled cell bodies in the brain-stem in two of the monkeys is shown in figs. 4 and 5. In all the animals in Group *c*, and in monkey No. 13 of Group *b*, there were numerous HRP-marked neurons in the raphé nuclei and the lateral, gigantocellular and N. reticularis pontis

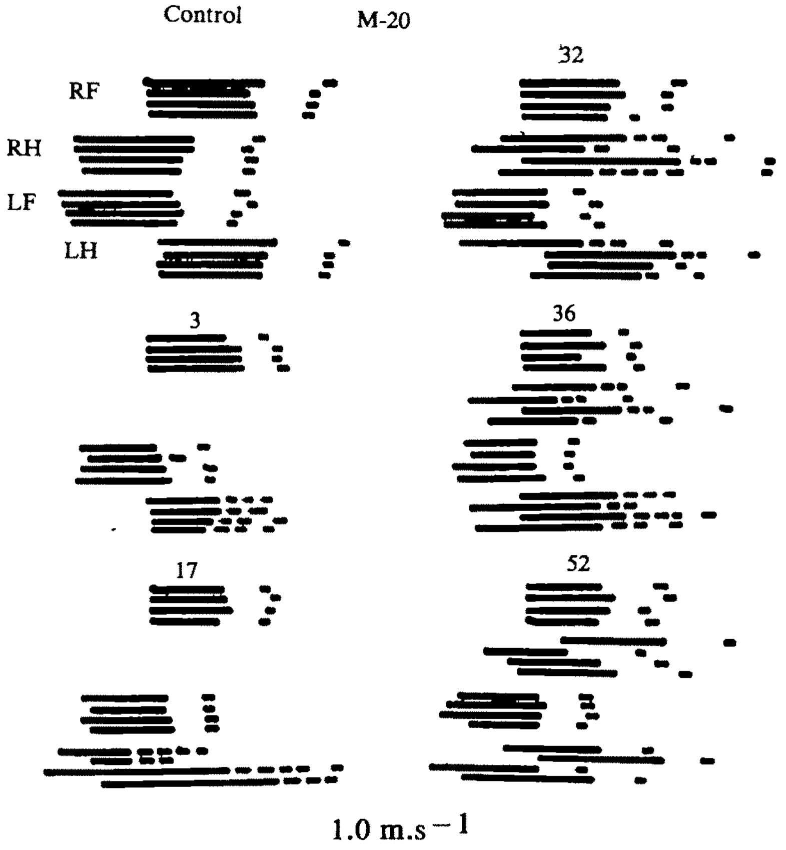

FIG. 3. Footfall pattern analysis of Monkey No. 20. Continuous line = stance phase. Dashed lines = swing phase without lift-off. Blank space to dot = swing phase with lift-off from belt. RF = right forelimb; RH = right hindlimb, etc. Sequences of four consecutive step cycles, aligned by floor contact of right forelimb. Numbers = days after spinal cord lesion. Recordings at up to twenty days taken with sling support of hindquarters, discarded later. No stepping by right hindlimb up to seventeen days (hemisected side). Notice absence of foot dragging after thirty-six days.

caudalis groups in the medulla and pons, with significant asymmetry between the two sides corresponding to the predominantly ipsilateral projection of the reticulospinal system (Kneisley, Biber and La Vail, 1978). In Monkeys 14, 18 and 20 the magnocellular group of the red nucleus was labelled in a crescent pattern, in the side opposite the spared dorsolateral fibres. We made no systematic observations of the labelling of cortical areas.

Group 4. Controlled Locomotion Experiments

The results of this experiment were consistent for all four subjects in that stepping activity in one or more limbs developed under the combined influence of treadmill motion and electrical stimulation of restricted loci in the CNS. Fig. 6 illustrates the distribution of 'positive' sites, which can be seen to cluster in the posterior subthalamic region and in the vicinity of N. cuneiformis and the superior cerebellar peduncle. The usual pattern of events, when the stimulating electrodes were in the loci with lowest threshold (25 to 100 μA), was as follows: at the lowest effective current intensity for that locus the contralateral hindlimb began stepping 2 to 5 seconds after the onset of the stimulus train and continued to step for 2 or 3 seconds

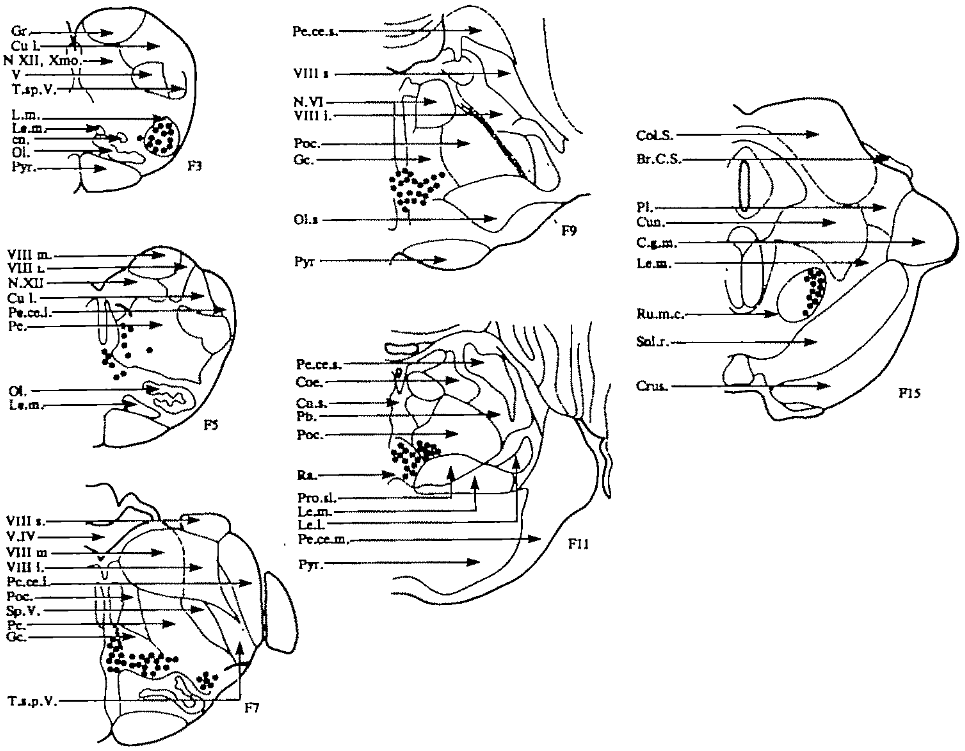

FIG. 4. Distribution of retrogradely labelled (HRP) cells in the brain-stem of a monkey that recovered after a partial cord section. Reconstructed on Oertel's (1969) atlas sections.

Key for figs. 4–5

Br.C.S.	Brachium colliculi superioris	Pc.	N. parvocellularis
C.g.m	N. Corporis geniculati medialis	Pe.ce.i.	Pedunculus cerebellaris inferior
cn.	N. centralis medullae oblongatae	Pe.ce.m.	Pedunculus cerebellaris medius
Cn.s.	N. Centralis superior	Pe.ce.s.	Pedunculus cerebellaris superior
Coe.	N. locus coeruleus	Pg.c.	N. paragigantocellularis
Col.i.	N. colliculi inferioris	Pl.	N. paralemniscalis
Col.s.	N. colliculi superioris	Poc.	N. reticularis pontis caudalis
Crus.	Crus cerebri	Pro.sl.	Processus griseum pontis supralemniscalis
Cu l.	Cuneatus lateralis		
Cun.	N. cuneiformis	Pul.	N. pulvinaris thalami
Fip.	Fossa interpeduncularis	Put.	Putamen
Fl.m.	Fasciculus longitudinalis medialis	Pyr.	Pyramis
Gc.	N. gigantocellularis	Ra.	N. raphes
Gr.	N. gracilis	Ru.m.c.	N. ruber, pars magnocellularis
Gr.cn.m.	Griseum centrale mesencephali	Ru.pc.	N. ruber, pars parvocellularis
Hipp.	Hippocampus	S.ni.	N. Substantia nigræ
Ip.m.	N. interpeduncularis medialis	Sni.cm.	N. Substantia nigræ pars compacta
Le.l.	Lemniscus lateralis	Sni.r.	N. Substantia nigræ pars reticularis
Le.m.	Lemniscus medialis	Sol.	N. tractus solitarii
Lgn.	N. geniculatus lateralis	Sp.V.	N. oralis tractus spinalis n. trigemini
L.m.	N. lateralis medullæ oblongatæ	T.sp.V.	T. spinalis n. trigemini
N.m.d.t.	N. dorsalis medialis thalami	V	N. tractus spinalis n. trigemini
N.v.p.l.	N. ventralis posterior lateralis thalami	V.mo.	N. motorius n. trigemini
N.VI	N. abducentis	VIII i.	N. vestibularis inferior
N.XII	N. n. hypoglossi	VIII m.	N. vestibularis medialis
Ol.	N. olivaris inferior	VIII s.	N. vestibularis superior
Ol.s.	N. olivaris superior	V.IV	Ventriculus quartus
Pb.	N. parabrachialis	Xmo	N. dorsalis motorius n. vagi

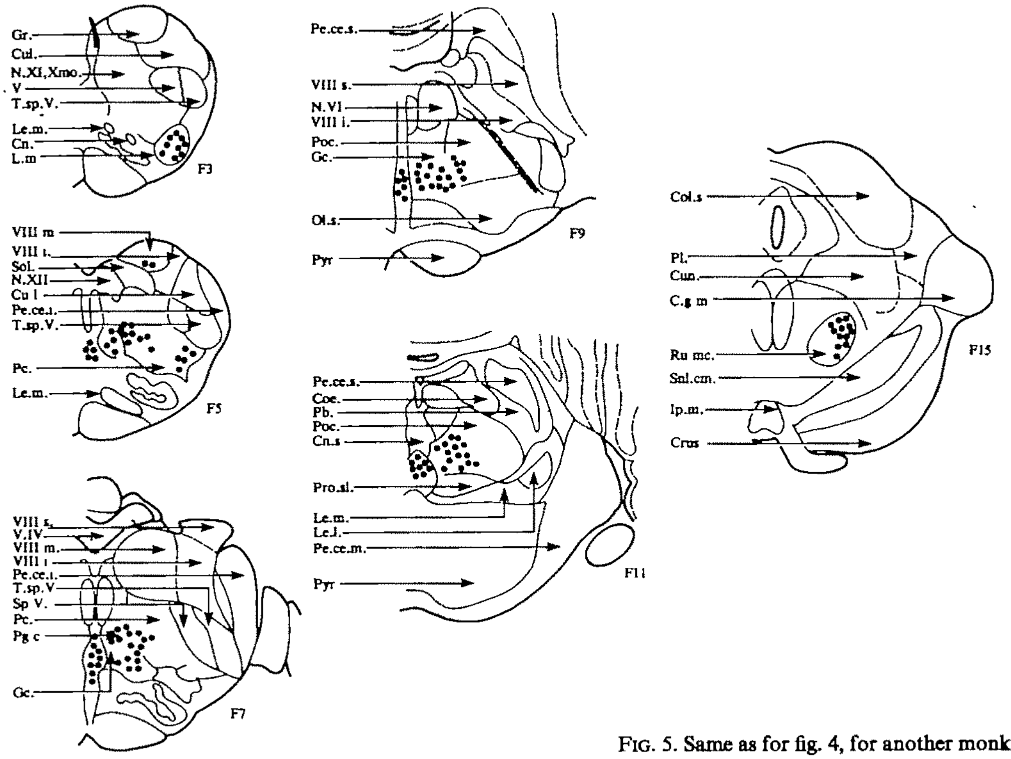

FIG. 5. Same as for fig. 4, for another monkey.

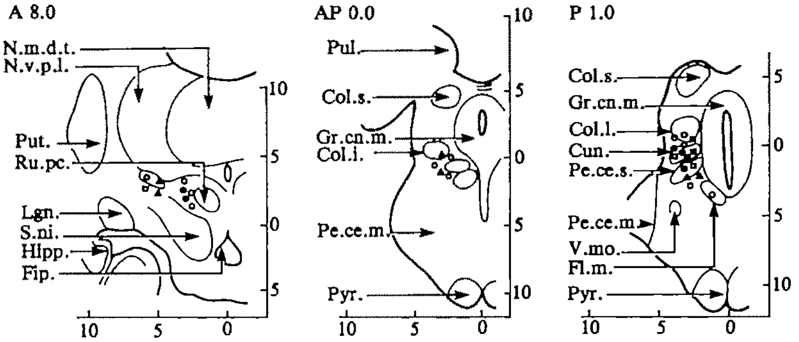

FIG. 6. Localization of electrode placements in three monkeys in Group 4 ('controlled locomotion' group). The stimuli were trains of undirectional rectangular pulses, each pulse 0.2 ms in duration, at a repetition rate of 50 pulses/s. The usual train duration was 5 s. The current flowed between the centre conductor and the outside barrel of the concentric pair of electrodes. Each symbol denotes a different monkey. Filled symbols = current per pulse between 25–100 μA. Open symbols = current per pulse between 100–200 μA. Higher threshold loci not indicated. These current ranges reflect the intensities required to initiate stepping by at least one limb (*see text* for consequences of higher stimulus intensities).

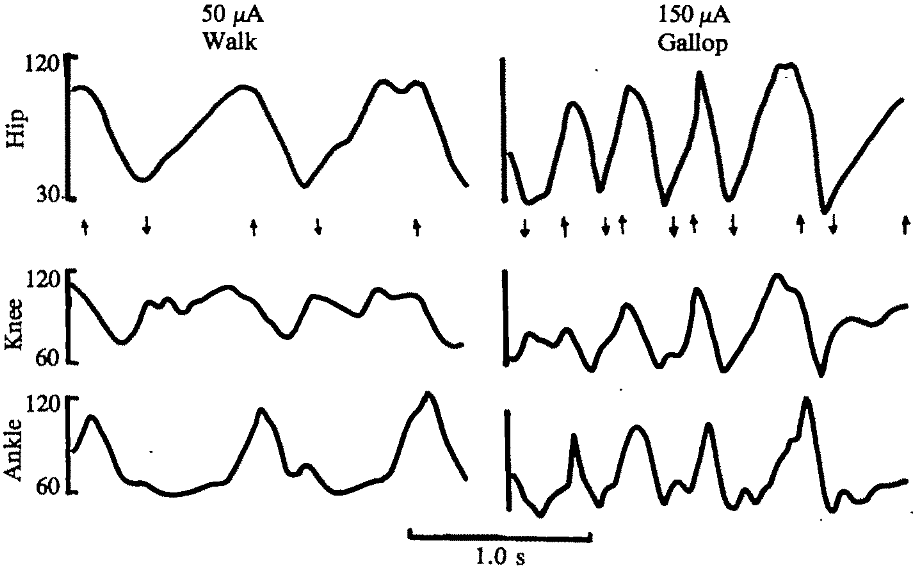

FIG. 7. Joint angle trajectories of the hindlimb of one monkey in Group 4. They show stepping activity at two different stimulus intensities indicated above. Continuous traces are interpolated, within 5 deg, from frame by frame (54 frame/s) measurements. Arrows, up = foot lift-off, down = belt contact.

after the end of the train. Stronger stimuli usually recruited the other hindlimb first and then the forelimbs with a rhythmicity resembling that of a slow walk. Still stronger stimuli, at the same repetition rate, caused the stepping rate to increase and then shift to a gallop pattern (fig. 7). This was usually contaminated by the generalized rigidity and body movements usually referred to as 'tegmental responses' (Ingram, Ranson, Hannet, Zeiss and Terwilliger, 1932). The sequence of limb movements during controlled locomotion was not simply alternating flexion and extension of the hip and shoulder joints, but included also properly sequenced motions of the other major limb joints, including a fast flexor 'flick' of the wrist which we have described previously in cats walking on a treadmill (Eidelberg and Yu, 1980). (Fig. 8.) We did not make any systematic observations on the possible modulation of the timing of the step cycle by changing belt speed. Movement of the belt alone, without electrical stimulation of the brain, did not evoke stepping. In another experiment (*see* Results, Group 1) we found that two thalamic monkeys, who had also been spinalized acutely and had been given a sequence of adjunctive drugs, walked on the moving treadmill with their forelimbs. Their stepping was rather stiff-legged compared to the monkeys in Group 4. Their hindlimbs did not move at all.

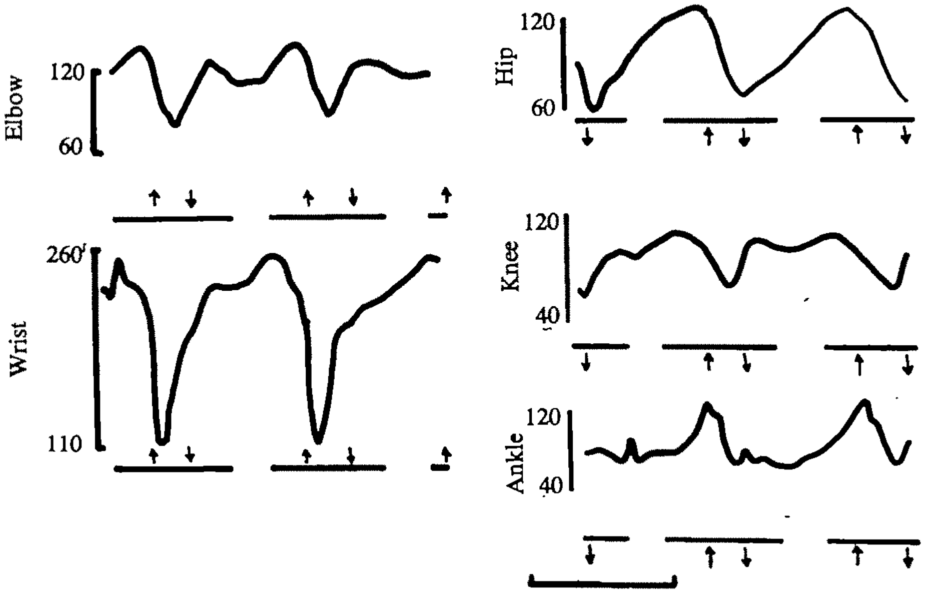

FIG. 8. Joint angle trajectories of the forelimb of a monkey in Group 4, showing stepping induced by brain-stem stimulation (N. cuneiformis). Notice the complex sequence of joint motions, including the rapid flexor flick of the wrist during the swing phase. Arrows indicate floor contact (down) and lift-off (up). Continuous lines represent floor contact by contralateral forefoot.

DISCUSSION

We carried out these experiments to test whether or not we could demonstrate 'spinal stepping' and 'controlled locomotion' in a primate. By the first we mean the production of rhythmical alternating movements by the muscles of the hindlimbs after spinal cord transection above the lumbosacral enlargement. We assumed that such activity would indicate the existence of an appropriate governing circuitry intrinsic to the cord. The demonstration of 'controlled locomotion' would support the hypothesis that there are 'centres' for co-ordinated progression in primates, as seems to be the case in other species.

As described in Results, our attempts at eliciting *spinal stepping* in macaque monkeys failed altogether, even though we used several methods which have elicited this phenomenon in cats, dogs and rabbits (Budakova, 1973; Eidelberg *et al.*, 1980; Forssberg and Grillner, 1973; Forssberg *et al.*, 1980; Freusberg, 1874; Grillner, 1973; Grillner and Zangger, 1979; Shurrager and Dykman, 1951; Viala and Buser, 1969, 1971). Immediately after spinal cord transection neither strong electrical stimulation of the dorsal columns (or, in two animals, of the ventral columns) nor administration of dopa plus adjunctive drugs (nialamide, R04-4602, 4-aminopyridine), nor a combination of both means, yielded alternating movements of the hindlimbs or their equivalent in electrical activity of the appropriate muscle nerves. It seemed unnecessary, therefore, to add dorsal root deafferentation to curarization to establish that stepping was not due to sequential reflex activation (*see* Grillner and Zangger (1979) for an excellent discussion of this issue). We considered the possibility that spinal shock, which in primates is manifested by a profound and long-lasting depression of segmental reflexes after spinal cord transection (and is very much milder and briefer in carnivores and other non-primate species), had so affected spinal cord neurons caudal to the transection that stepping activity was abolished as a consequence. However, recovery from spinal shock, evidenced by the return and even exaggeration of tendon and flexor reflexes, did not bring with it recovery of stepping. We considered the possibility that monkeys might not have a noradrenergic system of descending connections as the substrate for the action of dopa and its adjuvants. This question had been tested with histofluorescence methods by Crutcher and Bingham (1978) in a closely related macaque (*M. mulatta*). They found a pattern of distribution of descending catecholamine-containing fibres quite similar to that of the cat and rat. There is now evidence that puts into question the necessity of such a projection system for locomotor control, since depletion of catecholamines from the cord does not prevent 'controlled locomotion' (Steeves *et al.*, 1980) or 'natural locomotion' (Morgan and Huffman, 1980). This is also in agreement with our inability to elicit stepping with clonidine, at times when we should have expected supersensitivity of denervation in the post-synaptic elements receiving noradrenergic terminals (Nygren and Olson, 1976).

The negative results in Groups 1 and 2 can be interpreted in several other ways: they could reflect unsuspected technical problems, but we have obtained spinal stepping in cats by the same methods. The age of the subjects could be a factor, since cats and dogs spinalized prior to the onset of spontaneous walking seem to step more effectively than animals who were adult when spinalized (Shurrager and Dykman, 1951), but adult spinal cats do show stepping under our experimental conditions (Eidelberg *et al.*, 1980). An alternative, which we cannot rule out *a priori*, is that monkeys do not possess spinal pattern generators for stepping. However, an appeal to separateness from other mammalian species should be based on further experimentation. Another hypothesis seems to us the most reasonable one at this time: 'step generators' do exist in primates, but their access to skeletomotor neurons may depend, more heavily than in cats, upon the presence of tonic descending facilitatory influences. This implies that alpha motoneurons may not be participants in, but only executors of, the presumed pattern generator circuits (*see* Miller and Scott, 1977, for an opposite view, *also* Feldman and Orlovsky, 1975). Finally, the clinical evidence is strongly in agreement with our findings in monkeys, in that there is no evidence of clear-cut stepping behaviour in humans after anatomically verified complete spinal cord transection (Holmes, 1915; Kuhn, 1950; Riddoch, 1917).

In a prior report from this laboratory we showed that sparing of at least one ventrolateral quadrant of the spinal cord (at the thoracic level) allowed the return of bilateral hindlimb locomotor activity (Eidelberg *et al.*, 1980). Steeves and Jordan (1980) evoked 'controlled locomotion', also in cats, and observed that bilateral section of the ventrolateral quadrants prevented it. These findings restrict the list of the essential descending locomotor pathways to the reticulospinal and vestibulospinal systems. It seems reasonable to conclude from the data from Group 3 in this report that there are significant analogies between cats and monkeys in this regard, as well as some differences. The analogies centre on the fact that the ventrolateral cord sector is crucial for the eventual return of locomotor activity, and that there seems to be a correlation between the sparing of reticulo- and vestibulospinal axons and recovery. From the evidence in the literature we had no reason to expect a significant role in locomotor recovery for the corticospinal tract (Kuypers, 1973; Lawrence and Kuypers, 1968), and such was the case. The presence or absence of spinal shock (that is, absence or severe reduction of reflexes caudal to the lesion) in our animals depended also upon the preservation of the ipsilateral ventrolateral quadrant. On the side where it was cut the hindlimb was paralysed and there was also loss of tendon reflexes, both effects lasting several days. The other hindlimb stepped readily, often from the first post-operative day; it did not lose tendon reflexes, and became capable of support and propulsion shortly after the operation. The initially paralysed hindlimb was slow in regaining stepping motion, and was clearly weaker than its homologue as regards support and propulsion. Two of the cases reported by Gordon Holmes in 1915 are relevant to these findings. These patients did not have prolonged spinal shock, both stepped with the lower limbs, and both were later found (at autopsy, after death from intercurrent complications) to have substantial sparing of the ventral funiculi at the site of injury.

The last issue was whether 'locomotor control areas' could be defined in the monkey by the demonstration of 'controlled locomotion'. As described in Results, this was the case: we obtained locomotor activity by stimulation of certain sites in the posterior subthalamic region, near the subthalamic nucleus, and of sites in the midbrain tegmentum in or near N. cuneiformis. The movements resembled those of 'natural' locomotion in the pattern of joint motions and the elicitation of gait conversions. The methods used do not allow us to ascertain the identity of the neuronal elements (cell bodies or axons) which were critical for the elicitation of controlled locomotion. Thus, we could not feel sure whether the superior cerebellar peduncle just ventral to the inferior colliculi, or N. cuneiformis, was the essential component of the mesencephalic locomotor region; the same applies to the posterior subthalamus. For our immediate purposes this was not a critical problem, but it seems important to define more precisely the anatomical organization of this locomotor control system.

SUMMARY

We carried out experiments on young adult macaque monkeys (*M. fascicularis*) in an attempt to establish whether or not primates possess a locomotor control system consisting of spinal pattern generators modulated by brain-stem locomotor regions. We could not induce 'spinal stepping' in our subjects after spinal cord transection. Sparing of pathways contained in the ventral sector of the white matter of the cord was sufficient for stepping and walking. 'Controlled locomotion' was elicited in thalamic monkeys by electrical stimulation of the posterior subthalamic region or the midbrain tegmentum just ventral to the inferior colliculi.

We conclude that there are significant homologies between this primate species and the cat regarding the probable existence of supraspinal locomotor control structures, but it seems that the presumed spinal step generators in monkeys depend more on supraspinal inputs than they do in cats.

ACKNOWLEDGEMENTS

We thank Professors D. G. Stuart and S. Grillner for their advice. This work was supported in part by NINCDC Grant NS 14546 and the Paraplegia Foundation of Arizona. E.E. is Medical Investigator of the Veterans Administration.

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(Received January 22, 1981)

Brain (1981) **104**, 665-699

THE 'ONE-AND-A-HALF' SYNDROME

ELECTRO-OCULOGRAPHIC ANALYSES OF FIVE CASES WITH DEDUCTIONS ABOUT THE PHYSIOLOGICAL MECHANISMS OF LATERAL GAZE

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INTRODUCTION

UNTIL recently there have been few studies on the 'one-and-a-half' syndrome, a peculiar lateral gaze palsy. C. Miller Fisher named this unusual syndrome when he presented the first clinicopathological report of it in 1967. It combines two defects of horizontal eye movements: a lateral conjugate gaze palsy in one direction ('one'), and in the opposite direction a paralysis of adduction by one eye resulting from an internuclear ophthalmoplegia ('and-a-half'). Thus, the complete form of the syndrome involves one eye which cannot deviate laterally from the midline and the other eye which can only be abducted from the midline.

This study adds 5 new cases to the 17 others previously reported in the literature. One of the 5, accompanied by serial sections of the pons, becomes the fifth case for which anatomical and pathological material is published. Unlike the previous studies, the present investigation used electro-oculograms to evaluate the complex oculomotor palsies of the syndrome. This technique differentiates between our 5 cases with 'one-and-a-half' syndromes, thus allowing us to distinguish the pontine lesions producing the syndrome in each. In the light of recent clinical and experimental data, the findings lead us to propose hypotheses about the physiological mechanisms underlying conjugate horizontal eye movements.

MATERIAL AND METHODS

Eye movements were recorded separately for each eye using direct current electro-oculography.

The following movements were studied: (a) voluntary horizontal and vertical saccades performed by the subject in response to orders; (b) horizontal foveal smooth pursuit movements elicited by a

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pendulum moving with an amplitude of 25 deg in each hemifield of ocular movement; (c) horizontal and vertical oculocephalic movements tested by rapid passive rotations of the head, with the eyes open; (d) optokinetic nystagmus elicited by using alternating black and white stripes, covering a large visual field (60 deg), which moved horizontally across a screen located 80 cm in front of the patient; (e) horizontal vestibular nystagmus elicited by using cold water caloric stimulations of each ear; (f) convergence provoked by instructing the patient to follow an object as it slowly approached his/her nose; (g) finally, possible nystagmus was looked for at the extreme positions of gaze.

Case 1

A 48-year-old hypertensive man entered the hospital on December 1, 1977 with a myocardial infarction. The neurological course of the disease began acutely on December 17, 1977 with the sudden onset of left hemiparesis, left lateral deviation of gaze, diplopia and right peripheral facial weakness. On clinical examination two days later, in addition to the oculomotor defect, the following symptoms were noted: slight sleepiness, left hemiparesis with the exception of the face, bilateral extensor plantar responses, complete left-sided sensory loss (including the face), mild right-sided facial sensory loss, slight cerebellar ataxia of the right upper limb, complete right peripheral facial nerve palsy, right reactive miosis, right-sided deafness and right-sided palatal myoclonus. A lumbar puncture on December 19, 1977 revealed hæmorrhagic cerebrospinal fluid with 99,000 red blood cells per mm^3 and 190 white blood cells per mm^3. The patient died suddenly on January 12, 1978 with all the neurological disturbances above still present.

Oculomotor findings on December 19, 1977. Ocular statics. The right eye remained in the midline and the left eye was slightly and permanently deviated towards the left (5 deg) at rest.

Horizontal eye movements. With any type and any direction of lateral eye movements the right eye remained fixed on the midline, while the left eye could only abduct from and return to the midline. The left eye never crossed the midline to the right with any attempted lateral movement.

The leftward voluntary saccade of the left eye was normal (fig. 1A). Because the eye returned to the midline by a remarkably slow voluntary movement (approximate velocity of 10 deg/s) it could not be called a 'saccade'.

Abduction of the left eye during foveal pursuit of a smoothly moving stimulus was saccadic, consisting of multiple small saccades regularly interrupted by pauses (without any slow movements toward abduction) (fig. 1B). Return to the midline during attempted smooth pursuit to the right was extremely slow; in fact the movement could not follow the stimulation and it progressed at an unvarying velocity of approximately 10 deg/s.

The oculocephalic movement (not recorded) was limited: while the left eye could reach the left lateral extreme and then return to the midline, it could not cross the midline toward the right.

A left-beating nystagmus was observed when the left eye was near the left position (fig. 1C). The nystagmus appeared after left lateral deviation of approximately 10 deg and its amplitude increased with greater deviation. The nystagmus vanished during far lateral deviation after several seconds and the left eye came to rest 20 deg medial from the extreme lateral position.

Horizontal optokinetic stimulation of either direction evoked a left-beating nystagmus in the left eye. The appearance of this nystagmus was analogous to that induced by the left lateral deviation (fig. 1D).

After caloric stimulation of the left ear, the left eye exhibited a left-beating nystagmus; in appearance it was similar to that nystagmus induced by left lateral deviation (fig. 1Ea). After caloric stimulation of the right ear, the amplitude of the left-beating nystagmus was clearly greater (fig. 1Eb). However, the eye did not cross the midline toward the right.

Vertical movements. Downward saccades were normal and upward saccades were small in amplitude. Pursuit and oculocephalic movements were partly saccadic.

Convergence. Convergence occurred but was of small amplitude for both eyes.

In summary, the main features of this patient's oculomotor syndrome were:

(1) a complete right conjugate gaze palsy for all lateral movements;

(2) a complete adductive paralysis of the right eye for all lateral movements with slight preservation of convergence for this eye;

(3) left-beating nystagmus of the left eye when this eye was near the left position;

(4) in the left eye an absence of all rightward saccades within the left hemifield of movement;

(5) very abnormal pursuit movement for the left eye in its left hemifield of movement.

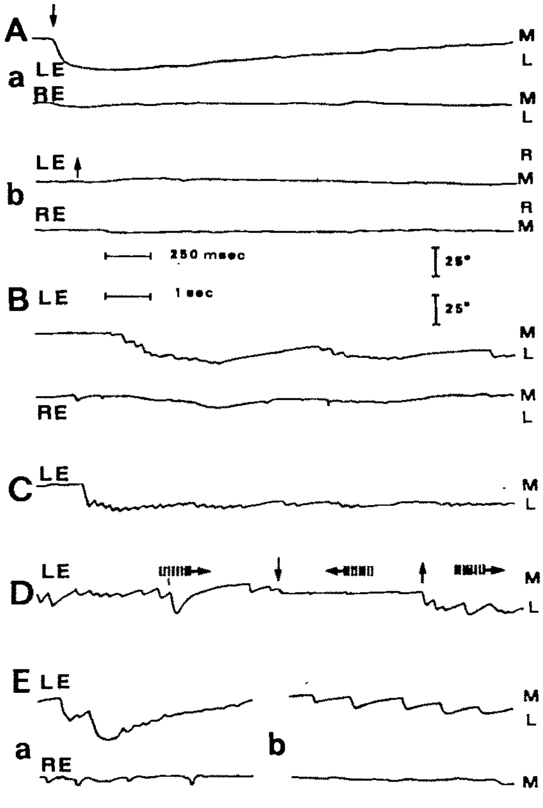

FIG. 1. *Horizontal eye movements, Case 1.* A downward deflection indicates an eye movement to the left and an upward deflection an eye movement to the right. L = left; M = midline; R = right. A, voluntary saccades. a, eye movements to the left: normal movement of the left eye (note the very slow return of the left eye to the midline); no movement of the right eye; b, eye movements to the right: none. B, foveal smooth pursuit movements. Movement of left eye is completely saccadic towards the left and very slow when the eye returns to the midline, which is not crossed. No movement of right eye. C, left-beating nystagmus of left eye is present in the left lateral position. D, optokinetic nystagmus (OKN) of left eye. Vertical arrows indicate changes of direction of the stimulation and horizontal arrows illustrate direction of the stimulation. Left OKN (right stimulation) of the left eye is rather similar to the nystagmus in C; right OKN (left stimulation) is absent. E, caloric stimulation. a, when the left ear is stimulated the nystagmus of the left eye is similar to the nystagmus in C; no actual movement of right eye; b, when the right ear is stimulated the nystagmus of the left eye has greater amplitude; no movement of right eye.

Pathological findings. Post-mortem examination was performed nine hours after death, and confirmed the presence of an anterolateral myocardial infarction.

Neuropathological examination was performed on coronal sections of the cerebral hemispheres and horizontal sections of the brain-stem. The entire pons was embedded in celloidin, cut serially and stained by hæmatoxylin and eosin, and Loyez stain for myelin.

The sections revealed a one-month-old pontine hæmorrhage which ruptured into the fourth ventricle. This hæmorrhage was limited to the right side of the pons and involved its entire length, sparing both the cerebral peduncles and medulla. The hæmorrhage mainly destroyed the pontine tegmentum (fig. 2), including the superior cerebellar peduncle, the medial lemniscus, the nuclei of the fifth, sixth and seventh cranial nerves, the locus coeruleus and pontine reticular formation (nucleus pontis centralis oralis, nucleus pontis centralis caudalis, nucleus papillioformis, processus griseum pontis supralemniscalis, nucleus subcoeruleus, nucleus parabrachialis lateralis and medialis). The external part of the medial longitudinal fasciculus was destroyed in the mid-pons (fig. 2, level B) and the lower fasciculus exhibited œdematous changes. The right paramedial part of the pontine tegmentum was not destroyed but was œdematous. The right ventral part of the pons was destroyed dorsally.

In summary, the hæmorrhage involved the right part of the pontine tegmentum including the right sixth nerve nucleus, the right pontine reticular formation and the right medial longitudinal fasciculus.

Case 2

A 49-year-old man presented with a history of intracranial hypertension for several months without any other neurological disturbances and underwent surgery on September 26, 1977 for an ependymoma of the fourth ventricle. The tumour was reached after vertically sectioning the lower third of the vermis, a necessary procedure due to the extension of the tumour into the lower part of the floor of the fourth ventricle. On the day following the operation, a left lateral gaze palsy, paralysis of adduction of the left eye, monocular nystagmus of the right eye, left peripheral facial weakness, complete lack of protrusion of the tongue and palsy of the vocal cords were observed. Seven months later on May 5, 1978, in addition to the originally identified neurological disturbances, a myoclonus of the palate and of the limbs was present.

Oculomotor findings on May 13, 1978. Ocular statics. At rest both eyes remained on the midline.

Horizontal eye movements. Bi-directional voluntary saccades of very small amplitude were noted in the left eye which barely crossed the midline. The rightward saccades of the right eye were normal (fig. 3A). The return of this eye to the midline was accomplished by successive small saccades. The right eye barely crossed the midline to the left.

The left eye moved very little during foveal pursuit movements. The right eye moved within its external hemifield in both directions by successive saccades (fig. 3B).

With oculocephalic manœuvres the left eye barely moved, while the right eye only moved within its external hemifield, the movements being saccadic in both directions (fig. 3C).

A right-beating nystagmus of large amplitude was observed in the right eye when it was near the right position (fig. 3A).

Optokinetic stimulation directed either to the right or to the left elicited neither a nystagmus (beside the one existing in the right deviation of the right eye) nor a slow deviation.

Caloric stimulations had no noteworthy effect.

Vertical eye movements. Voluntary saccades were normal; pursuit and oculocephalic movements were totally saccadic.

Convergence. Movement was normal for both eyes.

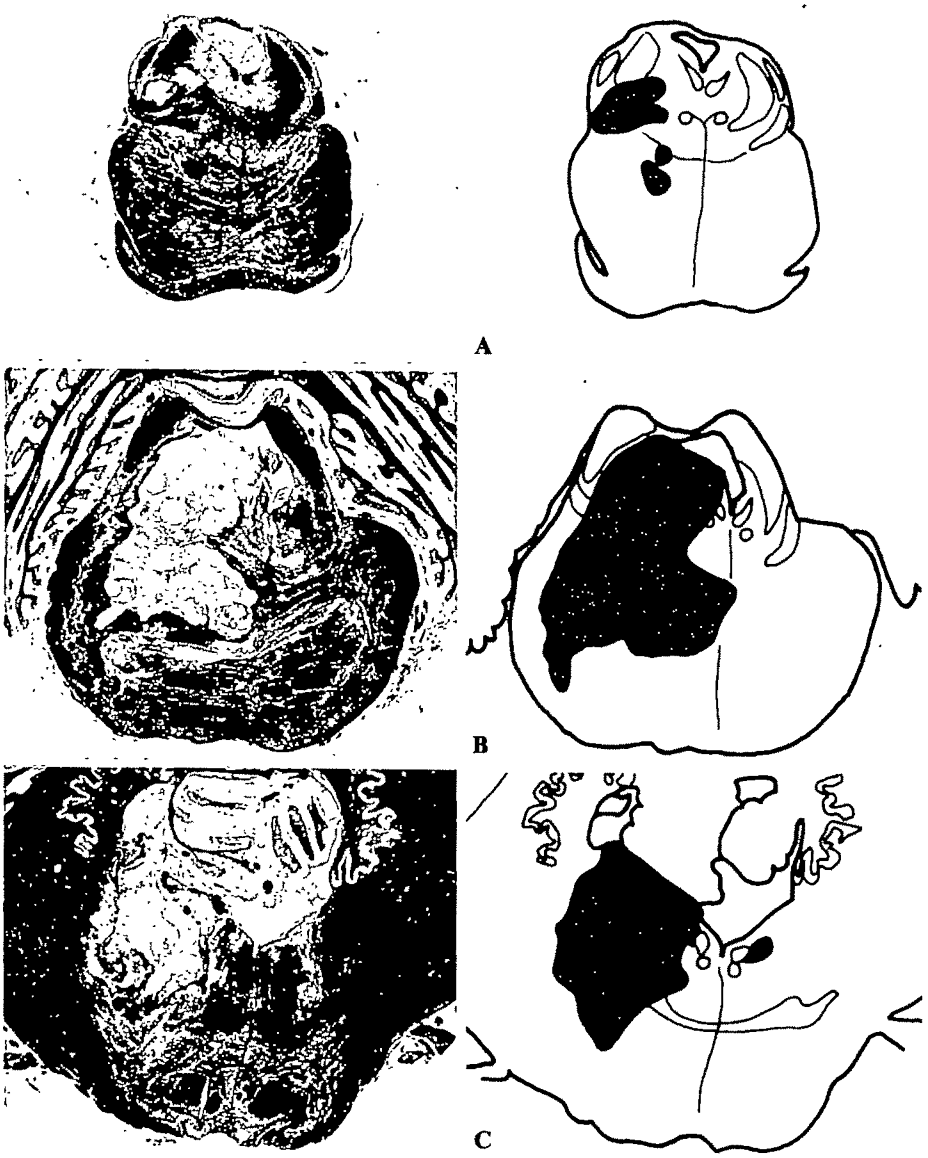

FIG. 2. *Anatomical pontine sections, Case 1.* The area where the hæmorrhage occurred is illustrated in grey. The structures outlined in black heavy lines are the fourth ventricle, the superior cerebellar peduncles, the medial longitudinal fasciculi, the medial tecto-spinal tracts, the abducens nuclei (black) the medial lemnisci and the dentate nuclei. A, upper pons. B, mid-pons, C, lower pons.

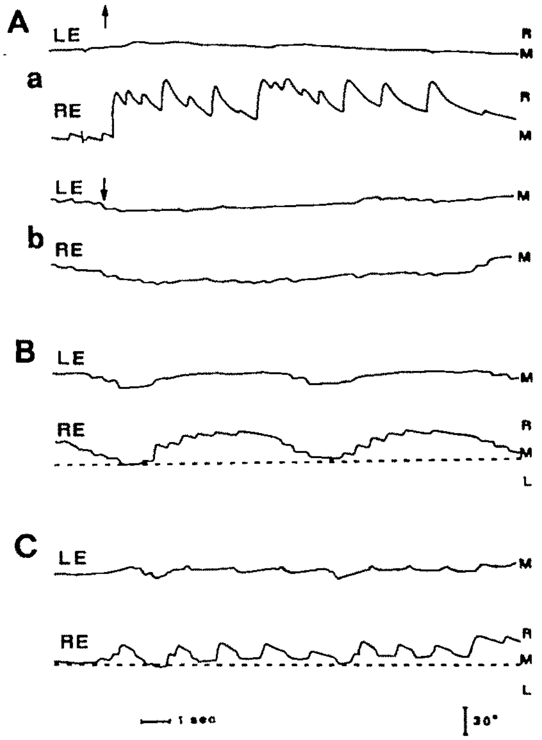

FIG. 3. *Horizontal eye movements. Case 2.* A, voluntary saccades. a, eye movements to the right: no movement of the left eye but normal movement of right eye; note the right-beating nystagmus of right eye present in the right lateral position; b, eye movements to the left: very slight movement of both eyes. B, foveal smooth pursuit movements. The left eye moves little. Right eye only moves from midline to right; the movements are saccadic, especially when the eye abducts. C, oculocephalic movements. The left eye moves little. Right eye only moves from the midline to right, in a saccadic manner.

In summary, the oculomotor syndrome for Case 2 consisted of:

(1) almost complete left conjugate gaze palsy for all lateral movements;

(2) complete adductive paralysis of the left eye for all lateral movements, with preservation of convergence;

(3) right-beating nystagmus of the right eye as this eye was near the right position;

(4) preservation of small leftward saccades as the right eye returned from the right lateral position to the midline;

(5) pursuit and oculocephalic movements of saccadic nature for the right eye in its external hemifield of movement and for both eyes in the vertical directions.

Case 3

In November 1977, a 29-year-old woman presented with paræsthesiæ of all four limbs and horizontal diplopia. She had been seen two years earlier with sensory changes of the left half of the body that had regressed within several weeks. Upon examination in December 1977, in addition to the oculomotor defect, a profound deficit of sensation in all four limbs was noted. The cerebrospinal fluid contained 23 lymphocytes per mm^3, 1 g/l protein with 19 per cent gamma gobulins. A diagnosis of multiple sclerosis was further supported by regression of the oculomotor signs approximately fifteen days later.

Oculomotor findings. (a) *First examination on December 5, 1977*

Ocular statics. At rest the right eye was in the midline and the left eye was slightly directed to the left.

Horizontal eye movements. The right eye remained in the midline for all attempted lateral saccades. The left eye had normal voluntary saccades to the left (300 deg/s), which decreased to 75 degs/s as the eye returned to the midline (fig. 4A). The left eye barely crossed the midline to the right.

Movements of the right eye were limited during foveal pursuit (fig. 4B). The left eye only moved from the midline to the left. As the eye abducted during pursuit stimulation, movement was saccadic yet

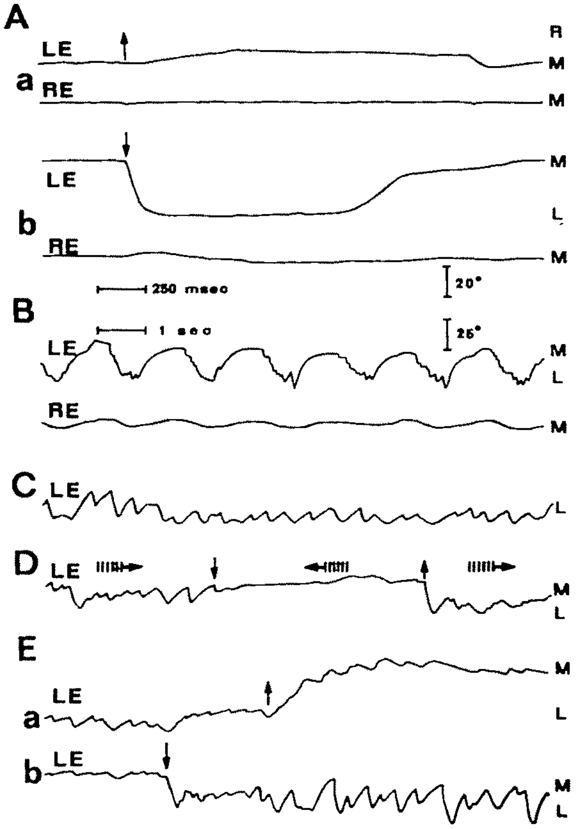

FIG. 4. *Horizontal eye movements, Case 3 (first examination).* A, voluntary saccades. a, eye movements to the right: very slight movement of left eye; no movement of right eye; b, eye movements to the left: normal movement of left eye (note slow return to the midline); no movement of right eye. B, Foveal smooth pursuit movements. The left eye only moves from the midline to left; to the left the movement is saccadic with some slightly smooth leftward components. Right eye is fixed. C, left-beating nystagmus of left eye is present in the left lateral position. D, optokinetic nystagmus of left eye. During stimulation to right the nystagmus of left eye is similar to the nystagmus in C. During stimulation to the left there is no movement. E, caloric stimulations. a, after stimulation of left ear the left-beating nystagmus of left eye in the left lateral position is similar to the nystagmus in C; close to the midline the nystagmus is reversed, with slower rapid phases to the right; b, after stimulation of right ear there is a little left-beating nystagmus of left eye in the midline and coarse nystagmus in the left lateral position.

retained, particularly medially, some leftward smooth components. The movement of the eye was smooth as it returned towards the midline. Its velocity varied and at times attained 30 deg/s.

Again, the right eye moved little with oculocephalic movements (not recorded). The left eye only moved from the midline to the left. As the eye abducted the movement was somewhat saccadic.

The left eye exhibited a left-beating nystagmus when it was near the left position (fig. 4C). Nystagmus appeared beyond a 10 deg lateral deviation.

During optokinetic stimulations the right eye remained fixed. During stimulation to the right, the left eye exhibited a left-beating nystagmus when the eye was near the left position, thus mimicking the nystagmus described above (fig. 4D). The midline was not crossed to the right. During stimulation to the left, the left eye remained fixed on the midline.

The right eye did not move when stimulated calorically. After caloric stimulation of the left ear, nystagmus was observed in the left eye but the direction of this nystagmus was variable (fig. 4Ea). Near the midline the quick phases of the nystagmus were directed to the right, slackened. Conversely, as the eye was near the left lateral position it exhibited the left-beating nystagmus described above and demonstrated in fig. 4C. Caloric stimulation of the right ear yielded a small amplitude nystagmus (quick phase directed to the left) in the left eye when it remained in the midline. This nystagmus had a large amplitude on attempted left fixation (fig. 4Eb).

Vertical eye movements. Voluntary saccades were normal; pursuit and oculocephalic movements were partially saccadic in both directions.

Convergence. Convergence was normal for both eyes.

In summary, the oculomotor syndrome on first examination consisted of:

(1) complete right conjugate gaze palsy for all lateral movements;

(2) complete adductive paralysis of the right eye for all lateral movements, with preservation of convergence;

(3) left-beating nystagmus of the left eye when this eye was near the left position;

(4) preservation of certain rightward saccades of the left eye within its external hemifield of movement.

(b) *Second examination, on December 20, 1977.* Paresis of abduction of the right eye persisted for all lateral movements. The eye could not move beyond 15 deg to the right. Adduction of this eye and lateral motility of the left eye were normal. However, when both eyes fixed in the left lateral position a small left-beating nystagmus, slightly greater in the left eye, appeared.

Case 4

A 75-year-old man, without any neurological history, presented with difficulty in looking toward the left which developed several days before attending hospital. Examination on February 1, 1979 showed a positive Babinski sign on the left without any motor deficit. The CAT scan revealed two separate small densities, approximately 1 cm in diameter, one in the anterior left temporal lobe and the other in the right anterior frontal lobe. Another density (0.5 cm in diameter) was noted in the left paramedian region of the pontine tegmentum (fig. 5). A history of surgical removal of a melanoma led to the diagnosis of metastatic tumours.

Oculomotor findings, on February 2, 1979. Ocular statics. Both eyes rested in the midline.

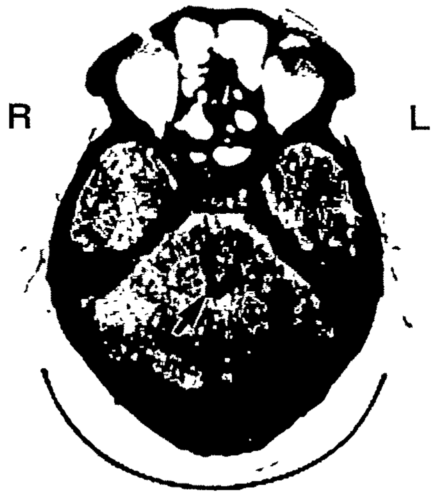

FIG. 5. *CAT scan, Case 4.* Section of lower pons. Note the metastatic tumour (darker) in left paramedian region of the tegmentum.

Horizontal eye movements. The left eye remained fixed in the midline during voluntary saccades (fig. 6A). Saccades of the right eye toward the right were normal. Voluntary return of the right eye to the midline was very slow (approximately 10 deg/s); the eye could not cross the midline with attempted saccades to the left.

During foveal pursuit movements, the left eye remained fixed in the midline, and the right eye could only move in the right hemifield of movement (fig. 6B). As the right eye abducted, pursuit movement was largely saccadic, although for very short distances there was smooth movement; return to the midline was slow (approximately 10 deg/s) at a constant velocity.

During the oculocephalic movements the left eye remained in the midline while the right eye moved freely reaching the extreme left position (fig. 6C). Movement of the right eye showed some saccadic features as the eye was abducting near the right lateral position.

A right-beating nystagmus was observed in the right eye when this eye was directed to the right beyond 20 deg laterally (fig. 6D).

During optokinetic stimulations the left eye remained fixed. Nystagmus similar to that described above appeared in the right eye during stimulation to the left (fig. 6E). The right eye remained fixed in the midline during stimulation to the right.

The left eye did not move after caloric stimulations. With stimulation of the left ear, the right eye in the right lateral position exhibited a nystagmus similar to the one shown in fig. 6D (fig. 6Fa). In addition, the right eye could voluntarily cross the midline toward the left with a very slow movement; at such a time it came approximately half-way between the midline and the left lateral extreme. After stimulation of the right ear a right-beating nystagmus (with an amplitude smaller than the one shown in fig. 6D), was seen at the midline and also with the eye positioned toward the right (fig. 6Fb).

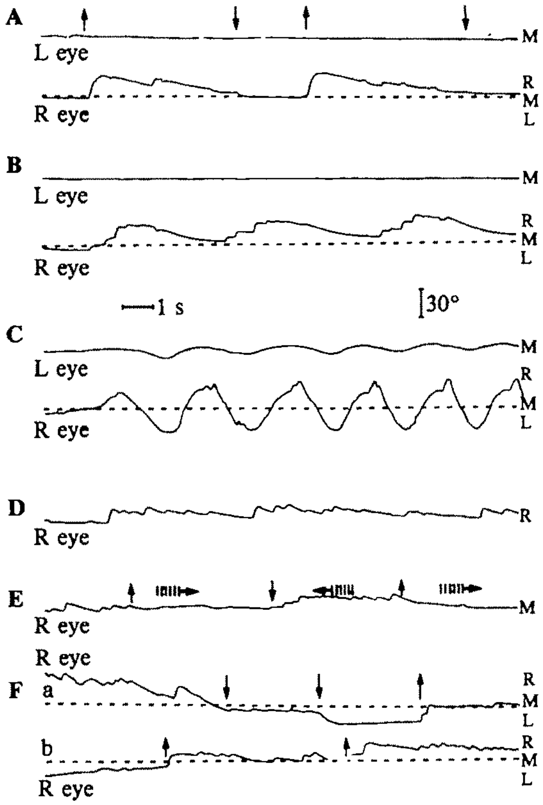

FIG. 6. *Horizontal eye movements, Case 4.* A, voluntary saccades. Left eye is fixed. Right eye moves only from the midline to the right; movement is normal to the right but very slow when eye returns to the midline. B, foveal smooth pursuit movements. Left eye is fixed. Right eye only moves from the midline to the right; movement is saccadic but with some rightward smooth components. C, oculocephalic movements. Left eye moves very little. Right eye has full range of motion. D, right-beating nystagmus of right eye is present in the right lateral position. E, optokinetic nystagmus of right eye. No movement with stimulation to the right. With stimulation to the left a right-beating nystagmus occurs which is similar to that illustrated in D. F, caloric stimulations (the vertical arrows indicate the changes of the fixation positions of the eye). After stimulation of the left ear the right eye can voluntarily cross the midline to the left (but the left extreme position is not reached). After stimulation of the right ear the right-beating nystagmus of the right eye is similar to the nystagmus in D.

Vertical eye movements. Voluntary saccades were normal. Pursuit movement was slightly saccadic in both directions. Oculocephalic movement was normal.

Convergence. Movement was depressed for both eyes.

In summary, the oculomotor syndrome included:

(1) left conjugate gaze palsy involving voluntary saccades and pursuit movements, with preservation in the right eye of the oculocephalic movement toward the left;

(2) complete abductive paralysis of the left eye for all lateral movements;

(3) complete adductive paralysis of the left eye for all lateral movements, with a limited ability to converge;

(4) right-beating nystagmus of the right eye, when this eye was near the right lateral position;

(5) absence of saccadic movements when the right eye returned from the right lateral extreme to the midline.

Case 5

A 70-year-old woman with no previous neurological symptoms presented with an acute onset of diplopia. Physical examination on January 16, 1980 did not reveal abnormalities other than oculomotor disturbances. Due to partial regression of the oculomotor syndrome during the next several days a tentative diagnosis of a cerebrovascular accident was made.

Oculomotor findings on January 16, 1980 (a) *Before caloric stimulation of the right ear.*

Ocular statics. At rest the right eye remained in the midline, and the left eye was directed 25 deg to the left of the midline.

Horizontal eye movements. The right eye was fixed when voluntary saccades were performed (fig. 7A). Leftward saccades of the left eye were normal. The drift back to the midline of the latter was slowed, and the eye barely crossed to the right of the midline.

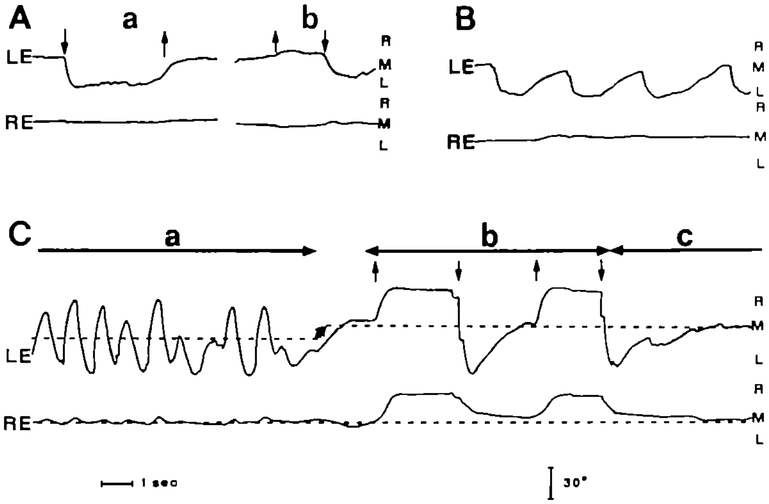

FIG. 7. *Horizontal eye movements, Case 5.* A, voluntary saccades (before caloric stimulation of the right ear). The right eye is fixed. a, movement of the left eye to the left is normal, but its motion is slowed in returning to the midline; b, there is almost no movement of the left eye to the right (the movement after the second arrow is again directed to the left). B, foveal smooth pursuit movements (before caloric stimulation of the right ear). The right eye is fixed. The left eye only moves from the midline to the left and the movement is saccadic to the left (with intermittent short smooth components). C, eye movements after caloric stimulation of the right ear. a, oculocephalic movements: the right eye moves very little (only in abduction) while the left eye exhibits a full range of movement; b, voluntary saccades: the saccades to the right are present for both eyes; only the left eye crosses the midline towards the left. c, a left-beating nystagmus of the left eye is present in the left lateral position.

The right eye did not move during foveal pursuit movements, and the left eye moved only in its left hemifield (fig. 7B). As the latter abducted, the movement was generally saccadic, but, especially when close to the midline, some portions of the movement were smooth.

Oculocephalic movements of the right eye included very limited abduction (10 deg) and no adduction. The left eye moved in the entire field of movement and reached the right extreme position.

A very slight nystagmus of the left eye was apparent when the eye was at the extreme left (fig. 7Aa).

During optokinetic stimulations, the right eye did not move. During stimulation to the right, the left eye developed a nystagmus similar to that described above. The left eye remained fixed in the resting position during stimulation to the left.

Vertical eye movements. Voluntary saccades were normal while the pursuit and oculocephalic movements were slightly saccadic.

Convergence. Convergence was weak for both eyes.

(b) *After caloric stimulation of the right ear the horizontal eye movements changed dramatically.*

Ocular statics. Both eyes were in the midline at rest.

Horizontal eye movements. The oculocephalic movements were identical with those seen prior to right ear caloric stimulation: the right eye abducted slightly and the left eye moved freely throughout its entire field of movement (fig. 7ca).

Although slightly slow, rightward saccades were present for both eyes which reached the extreme right position. The leftward saccade of the left eye was normal; yet, the right eye could not cross the midline to the left during the same movement (fig. 7cb).

A left-beating nystagmus in the left eye was observed as this eye was near the left lateral position (fig. 7cc).

(c) *After caloric stimulation of the left ear*, the horizontal eye movements were identical with those described before any manipulation.

In summary, the oculomotor symptoms included:

(1) tonic deviation of the left eye to the left which vanished after caloric stimulation of the right ear;

(2) paresis of right saccades;

(3) absence of horizontal oculocephalic movements by the right eye, while those of the left eye were normal;

(4) complete adductive paralysis of the right eye for all lateral movements with preservation of a weak convergence ability;

(5) left-beating nystagmus of the left eye in the left lateral position.

DISCUSSION

The first 3 cases in this study are classical examples of the 'one-and-a-half' syndrome (Fisher, 1967), in which horizontal movements are absent in one eye which remains fixed in the midline while the other eye is only capable of abduction from the midposition. The other 2 cases differ from the classical description in that both exhibit a dissociated conjugate gaze palsy ipsilateral to the lesion (namely, a palsy only for certain lateral movements). However, it must be emphasized that all cases show a failure of lateral conjugate gaze in one direction combined with a loss of adduction in the other direction. The basic preservation of most vertical eye movements and of convergence suggests the sparing of motor fibres and the nuclei of the third cranial nerves.

The causes of the syndrome are varied. Of the 17 cases found in the literature there were 4 proven and 5 probable infarctions, two gliomas, two astrocytomas, one arteriovenous malformation, two hæmorrhages and one probable case of multiple sclerosis (Bender and Weinstein, 1939; Freeman, Ammernan and Stanley, 1943; Reuben and Gonzales, 1964; Enoksson, 1965; Fisher, 1967; Sharpe, Rosenberg, Hoyt and Daroff, 1974; Kommerell, 1975; Crevits, de Reuck and Vander Eecken, 1975; Masson, Prier, Henin, Dairou and Pierrot-Deseilligny, 1978; Smith, Buchsbaum and Masland, 1980). In the present study, origins of the syndrome were a hæmorrhage, an ependymoma, a metastatic tumour, a probable infarction and a probable case of multiple sclerosis. Surely other ætiologies exist since the 'one-and-a-half' syndrome usually results from a single, unilateral and relatively small lesion of the dorsal tegmentum in the lower pons. First of all, the abducens nucleus (VI) and/or the pontine reticular formation (which is located rostrally and ventrally to this nucleus) are damaged by this lesion and an ipsilateral conjugate gaze palsy is produced. Secondly, damage by the same lesion to the ipsilateral medial longitudinal fasciculus, which lies at the same level or just above the abducens nucleus, accounts for unilateral internuclear ophthalmoplegia (i.e. the adductive paralysis of the fixed eye and the 'ataxic' nystagmus of the opposite eye).

To begin with, we shall analyse the two constituents of the syndrome, the lateral gaze palsy and the internuclear ophthalmoplegia, clinically and anatomically. Subsequently, a more detailed interpretation of the different lateral movements—saccades, foveal smooth pursuit and oculocephalic movements—will be presented to provide the basis for the development of some hypotheses about physiological mechanisms.

I. Clinical and Anatomical Considerations

A brief review of the recent clinical and experimental literature concerning the organization of lateral ocular motility in the brain-stem serves as a useful introduction to the structural and functional correlates of the 'one-and-a-half' syndrome.

Extensive experimental data from cats and monkeys suggest that the abducens nucleus contains both motoneurons of the lateral rectus and excitatory internuclear neurons that decussate at the level of the nucleus, ascend in the contralateral medial longitudinal fasciculus and terminate in the medial rectus subdivision of the oculomotor nuclear complex (Graybiel and Hartwieg, 1974; Baker and Highstein, 1975; Büttner-Ennever and Henn, 1976; Graybiel, 1977; Delgado-Garcia, Baker and Highstein, 1977; Highstein and Baker, 1978; Steiger and Büttner-Ennever, 1978; Bienfang, 1978; Steiger and Büttner-Ennever, 1979; Carpenter and Batton, 1980). The crucial role of the abducens nucleus for conjugate horizontal ocular movements was not recognized for a long time, even though it was supported by an old and unfortunately poorly detailed clinicopathological case (Bennett and Savill, 1889). That case report describes a complete unilateral conjugate gaze palsy (not only a paralysis of abduction) in conjunction with a minute infarction of the ipsilateral abducens nucleus. More recently, Carpenter, McMasters and Hanna (1963), after selectively damaging the abducens nucleus in monkeys, observed an ipsilateral gaze palsy for all lateral eye movements (including reflex movements). Carpenter's study also documented that certain ipsilaterally directed movements, particularly vestibular saccades, were still present in the contralateral hemifield of ocular movements.

The importance of the medial longitudinal fasciculus for adduction in lateral conjugate eye movements has been well documented over the years by numerous studies (Spiller, 1924; Bender and Weinstein, 1944; Cogan, Kubik and Smith, 1950; Carpenter and McMasters, 1963; Harrington, Hollenhorst and Sayre, 1966; Cambier, Masson and Lechevalier, 1972; Evinger, Fuchs and Baker, 1977). As stated above, the portion of the medial longitudinal fasciculus lying between the nuclei of the sixth and the third nerves contains axons of excitatory internuclear neurons which synapse with medial rectus motoneurons. One deduces that these internuclear neurons are necessary for any type of horizontal movement, since adduction (except for convergence) is suppressed in complete forms of internuclear ophthalmoplegia. Furthermore, the experimental studies of King, Lisberger and Fuchs (1976) and Pola and Robinson (1978) show that such neurons mediate both burst and tonic signals during all lateral conjugate eye movement. At present, the place of these excitatory neurons is presumed to be exclusively for the mechanism of conjugate lateral movements at the level of the oculomotor nuclear complex since the functional utility or the existence of inhibitory ascending tracts which synapse with the medial rectus motoneurons is doubted (Baker and Highstein, 1978; Pierrot-Deseilligny, Rigolet and Chain, 1979; Uchino, Suzuki, Miyazawa and Watanabe, 1979; Nakao and Sasaki, 1980; Grantyn, Grantyn, Gaunitz and Robine, 1980; Hikosaka, Igusa and Imai, 1980).

Numerous experimental studies in monkeys have produced data supporting the primary importance of the pontine reticular formation in the integration of horizontal conjugate gaze. Electrical stimulation of the pontine reticular formation induces ipsilateral ocular deviations while stereotaxic lesions provoke ipsilateral gaze palsies (Teng, Shanzer and Bender, 1956; Bender and Shanzer, 1964; Cohen, Komatsuzaki and Bender, 1968; Goebel, Komatsuzaki, Bender and Cohen, 1971). The pontine reticular formation contains two main types of neurons associated with eye movements (Sparks and Travis, 1971; Luschei and Fuchs, 1972; Keller, 1974; Kubo, Matsunaga and Hayshi, 1978). The phasic cells are active during saccades, namely all the rapid eye movements (voluntary saccades and quick phases of nystagmus). The tonic cells are active during fixation and slow eye movements (mainly smooth pursuit and the slow phases of nystagmus). The pontine reticular formation is connected to the ipsilateral abducens nucleus by an excitatory pathway

(Büttner-Ennever and Henn, 1976; Highstein, Maekawa, Steinacker and Cohen, 1976), probably involving a relay close to the nucleus itself (Maciewicz, Eagen, Kaneko and Highstein, 1977; Gacek, 1979; Igusa, Sasaki and Shimazu, 1980). In the cat it has been suggested that such an excitatory pathway could arise from the border zone between the oral and caudal subdivisions of the nucleus pontis centralis which is located rostrally and ventrally to the abducens nucleus (Graybiel, 1977). No direct inhibitory pathway exists from the pontine reticular formation projecting to the contralateral abducens nucleus (Highstein *et al.*, 1976). However, there is an inhibitory pathway from each pontine reticular formation that travels through the giganto-cellular tegmental field located caudal and close to the ipsilateral abducens nucleus, crosses the brain-stem and terminates in the contralateral abducens nucleus (Hikosaka and Kawakami, 1976, 1977; Graybiel, 1977; Maciewicz *et al.*, 1977; Gacek, 1979). The importance of this pathway has been demonstrated for saccades (Hikosaka and Kawakami, 1977; Hikosaka *et al.*, 1980; Yoshida, McCrea, Berthoz and Vidal, 1980), but the existence of an analogous pathway to control slow movements is still uncertain. In any case, the pontine reticular formation acts as the final supranuclear centre for lateral movement, either voluntary or pursuit. It generates all ipsilaterally-directed saccades, including the quick phases of vestibular nystagmus, in the entire field of lateral movements (Cohen *et al.*, 1968; Goebel *et al.*, 1971; Pierrot-Deseilligny, Prier, Masson and Cambier, 1978; Pierrot-Deseilligny, Chain, Gray, Escourolle and Castaigne, 1979). In addition, it may be involved in the control of the ipsilateral smooth pursuit movement, not only for the ipsilateral hemifield but also, as will be discussed further, for the contralateral hemifield. Only the oculocephalic movement partly escapes its control (Halsey, Ceballos and Crosby, 1967; Pierrot-Deseilligny *et al.*, 1978; Pierrot-Deseilligny, Chain, Gray, Escourolle and Castaigne, 1979), because certain vestibular tracts project directly to the vestibular nuclei (Lorente de Nó, 1933; Szentágothai, 1950; Carpenter, 1971; Cohen, 1971; Baker and Highstein, 1975; Hikosaka, Maeda, Nakao, Shimazu and Shinoda, 1977). Consequently, the two important clinical features of the unilateral pontine reticular formation damage are (Pierrot-Deseilligny, Chain, Gray, Escourolle and Castaigne, 1979): (1) a dissociated ipsilateral conjugate gaze palsy, in which only oculocephalic movement is preserved ipsilaterally permitting both eyes to be driven beyond the midline to the side of the lesion; (2) the loss of all ipsilaterally-directed saccades within the contralateral hemifield of movement.

Lateral gaze palsy. Theoretically, there appear to be four possible mechanisms of the lateral gaze palsies that can be observed in the 'one-and-a-half' syndrome as illustrated by our first four cases. The fifth case appears to present a variation of the fourth. The lateral gaze palsy may be produced by damage of both the pontine reticular formation and the abducens nucleus (Case 1), only the abducens nucleus (Case 2), both the root fibres of the abducens nucleus and the contralateral medial longitudinal fasciculus (assuming that two distinct lesions exist) (Case 3), or only the pontine reticular formation (Case 4). Each variation demonstrates distinctive clinical features.

In Case 1, a right pontine hæmorrhage destroyed the right medial longitudinal fasciculus, the abducens nucleus and the pontine reticular formation. Since both eyes never did cross the midline to the right, including the oculocephalic manœuvre, damage to the right abducens nucleus could be suspected prior to the post-mortem study. Also, the absence of saccades toward the right (including the vestibular quick phases) in the left hemifield of ocular movement indicated damage to the right pontine reticular formation.

In the second case, a lateral gaze palsy to the left for all movements again suggested the involvement of the left abducens nucleus. Presumably, the left pontine reticular formation was preserved since saccades toward the left, as in the pursuit movements, persisted in the right hemifield of movement. It would be reasonable to assume that a lesion of the floor of the fourth ventricle in the lower pons only affected the dorsal part of the tegmentum (that is, the abducens nucleus and medial longitudinal fasciculus), sparing the more ventrally located PRF.

In the third case, a complete right lateral gaze palsy was present at the first examination, and vestibular saccades toward the right could be evoked in the left hemifield of movement. As in the previous case, this combination suggested that the right abducens nucleus was damaged and that the pontine reticular formation was spared. Therefore, the involvement of the right medial longitudinal fasciculus was sufficient to explain the 'one-and-a-half' syndrome. However, the presence of two lesions is supported in this case, one lesion affecting the medial longitudinal fasciculus bilaterally and the other involving the root fibres of the right abducens nucleus. Two weeks after the first examination only an abductive paralysis of the right eye for all lateral movements persisted; this symptom by itself is only consistent with an interruption of the abducens fibres (Pierrot-Deseilligny and Chain, 1979) along their pontine course since the presumptive diagnosis in this third case was multiple sclerosis. Thus, the permanent conjugate feature of a lateral gaze palsy, or conversely, its disconjugate characteristic present during its evolution, give the best clinical basis for locating the lesion(s). A lateral gaze palsy can result from one lesion damaging the abducens nucleus and the somas of both types of neurons involved in the lateral gaze. An identical palsy can also be produced, however, by damage to the axons of the same neurons within their course through the brain-stem, namely, the fibres of the abducens nucleus and those ascending in the contralateral medial longitudinal fasciculus; the separation of these two sites suggests two lesions. A lateral gaze palsy which always remains conjugate during its clinical evolution is consistent with the first possibility, while one that is not conjugate at any time during its evolution would better fit the second.

In the fourth case, the left conjugate gaze palsy was dissociated since the right eye reached the extreme left position during the oculocephalic manœuvre. The latter indicates integrity of the left abducens nucleus. Inasmuch as all saccades directed to the left were abolished within the right hemifield of movement, it appears likely that the left pontine reticular formation was damaged. The only apparent explanation for the lack of oculocephalic movement of the left eye toward the left is the concurrent damage to the fibres of the left abducens nucleus at the pontine level. We reported the latter previously in a study for which pathological analysis was available (Pierrot-Deseilligny, Chain, Gray, Esourolle and Castaigne, 1979). The CAT scan in the present case gave a picture which was consistent with a lesion in the left paramedian pontine tegmentum involving the left pontine reticular formation along with the fibres of the left abducens nucleus (which pass through the lower part of this formation), and probably with the left medial longitudinal fasciculus at the posterior corner of the lesion (fig. 5). The abducens nucleus itself was spared and consequently retained its direct afferent pathways, arising from the vestibular nuclei and accounting for the preservation of the right eye's oculocephalic deflection to the left.

In the fifth case, as in the fourth, the lateral gaze palsy was probably a result of damage to the ipsilateral pontine reticular formation. At the initial oculomotor examination a tonic deviation of the left eye to the left was noted while the right eye remained in the midline. During the first days following a cerebrovascular accident affecting the brain-stem, this kind of monocular deviation, labelled 'paralytic pontine exotropia' by Sharpe *et al.* (1974), is usually observed. It is likely that our case had had a minute infarction two days prior to the oculomotor examination. The left eye did not cross beyond the midposition in attempted voluntary or pursuit movements to the right. Moreover, the left eye moved to the right extreme position during oculocephalic movement while the right eye remained in midline (with any type of horizontal movement). Thus, as in the previous case, at this stage of the examination, it was deduced that there was a right internuclear ophthalmoplegia in addition to the severe damage of both the ipsilateral pontine reticular formation and fibres of the abducens nucleus, but no damage to the abducens nucleus itself. However, stimulation of the caloric reflexes by placing cold water in the right ear completely changed the oculomotor syndrome and our thinking about the lesion's possible location. After such stimulation, the right eye still remained in the midline while the left eye approached the midposition, partly overcoming the left tonic deviation. Furthermore, both eyes moved to the extreme right position with slightly slow voluntary saccades. This showed both that the right pontine reticular formation was partly preserved and that the root fibres of the abducens nucleus were undamaged.

It thus appears that the 'one-and-a-half' syndrome includes four main types of lateral gaze palsies which have been correlated to different lesion locations through the use of electro-oculographic recordings of clinical features. The internuclear ophthalmoplegia, always responsible for the adductive paralysis of the more or less fixed eye, is the common feature of our five cases, and of all 'one-and-a-half' syndromes.

Internuclear ophthalmoplegia. The internuclear opthalmoplegia includes a paralysis of adduction of one eye, usually with preservation of convergence, and an 'ataxic' nystagmus of the other eye in abduction. As already mentioned, numerous clinical and experimental studies have indicated that this syndrome results from damage to the ipsilateral medial longitudinal fasciculus between the sixth and third nerve nuclei. The first case showed that involvement of the medial longitudinal fasciculus in the pontine tegmentum above the abducens nucleus correlated with the adductive paralysis of the fixed eye. In the four other cases the adductive palsy of the fixed eye during all types of lateral movements and the preservation of the convergence suggest the existence of an internuclear ophthalmoplegia, which can be taken to imply a lesion of the ipsilateral medial longitudinal fasciculus. This postulate is further supported by other typical disturbances of an internuclear ophthalmoplegia in the opposite eye.

Nystagmus was observed in the eye opposite the lesion. This nystagmus was not present during midline positioning but became visible with 10 to 20 deg lateral deviation, its amplitude increasing with increased deviation. Furthermore, when the same eye was abducted by any slow movement, defects identical to those we previously described were noted (Pierrot-Deseilligny and Chain, 1979). These impairments consisted of a saccadic pursuit movement, a more or less saccadic oculocephalic movement, and lack of the slow phases of the optokinetic and vestibular nystagmus. As the eye returned toward the midline from the lateral position, the various slow movements were less affected, except for those of the second case in which they were completely disorganized. No anatomical basis for this disorganization can be provided since the borders of the lesion are not defined. We have suggested the 'ataxic' nystagmus and disturbances of all slow movement of the abducting eye could be elicited by a permanent failure to excite the ipsilateral abducens nucleus (Pierrot-Deseilligny and Chain, 1979). The failure of excitation could result from one lesion interrupting not only the excitatory internuclear neurons ascending to the medial rectus motoneurons, but also a pathway descending close to the medial longitudinal fasciculus from the area of the third nerve nucleus and terminating in the opposite abducens nucleus (after a decussation at this level). Possibly mediating a reticular activity—or a vestibular activity, *via* the ascendant tract of Deiters (Reisine and Highstein, 1979) and axon collaterals of the medial rectus motoneurons (Evinger, Baker and McCrea, 1979)—this descending pathway could connect at the pontine level with functional units for fixation and slow ocular movements. Extensive morphological studies in the cat attest to the existence of such a pathway (Graybiel and Hartwieg, 1974; Maciewicz, Kaneko, Highstein and Baker, 1975; Graybiel, 1977; Maciewicz and Spencer, 1977; Edwards and Henkel, 1978; Gacek, 1979). Bender (1980) and de Jong, Cohen, Matsuo and Uemera, (1980) think as we do (Pierrot-Deseilligny and Chain, 1979), that its interruption could explain ataxic nystagmus. It was suggested by Edwards and Henkel (1978), however, that the descending pathway might mediate inhibitory impulses for convergence to both abducens nuclei. According to Gonzales and Reuben's electromyographic data (1967) this concept seems improbable since even with bilateral medial longitudinal fasciculus damage complete relaxation of the lateral rectus occurs during convergence. At this point, the exact physiological role of the interneurons connecting the area of the third nerve nucleus with the opposite abducens nuclear region is still to be determined.

II. Physiological Deductions on the Mechanisms of Lateral Eye Movements

Our electro-oculographic recordings lead us to propose certain hypotheses about the physiological mechanisms of the different lateral eye movements. The discussion will consider the saccades, foveal smooth pursuit movements and oculocephalic movements.

Saccades. As in the case with any eye movement, a saccade results from the contraction of the agonist muscles and the relaxation of the antagonist muscles. The neurons controlling the agonist muscles are subject to excitation arising from the phasic (or burst) cells of one pontine reticular formation (Van Gisbergen, Robinson and Gielen, 1981), while the neurons of the antagonist muscles are inhibited by the same pontine reticular formation. These two physiological processes take place at the level of the abducens nuclei for conjugate lateral gaze (Pierrot-Deseilligny and Chain, 1979; Hikosaka *et al.*, 1980). For the vestibular saccades (as probably for all types of saccades) the excitatory afferent pathways terminating in one abducens nucleus emanate from the ipsilateral pontine reticular formation, while inhibitory afferent pathways originate from the contralateral pontine reticular formation and pass *via* the contralateral giganto-cellular tegmental field (Hikosaka and Kawakami, 1977; Yoshida *et al.*, 1980).

In the present cases, the pontine reticular formation and abducens nucleus contralateral to the lesions remained undamaged, accounting for the integrity of saccades produced by the abducting eye. The agonist muscle of the abducting eye receives normal phasic excitation from these structures. Saccades from the midline to the side of the lesion are abolished in our four first cases because of damage to the ipsilateral abducens nucleus and/or the pontine reticular formation (Cases 1, 2 and 4), or to motoneuron fibres of the abducens nucleus and the contralateral medial longitudinal fasciculus (Case 3). In all cases there is no phasic excitation to the agonist muscles. In the fifth case the saccades ipsilateral to the lesion are slower than normal because the pontine reticular formation may be slightly damaged. As the abducting eye returns to the midline in a voluntary movement directed to the side of the lesion, only the antagonist muscles are functioning and the velocity of the movement is always impaired. In the first and fourth cases which include an involvement of the pontine reticular formation ipsilateral to the lesion, a very slow movement, lasting more than ten times the normal time, has taken the place of the voluntary saccade returning to the midline. In addition the optokinetic and vestibular saccades, which should occur in the same direction in this hemifield of movement, are lost. These findings can be explained by the lack of phasic inhibition from the damaged pontine reticular formation. The preservation of a very slow voluntary movement returning the eye to the midline is probably due to suppression of excitation (disfacilitation) from the tonic cells of the undamaged pontine reticular formation controlling the eye position (Pierrot-Deseilligny, Chain, Gray, Escourolle and Castaigne 1979). In the second and third cases the pontine reticular formation ipsilateral to the lesion is probably preserved since weak saccades, directed from the outer boundary to the midposition, were present during pursuit movements (in the second case) and after the caloric stimulation (in the third case). In the third case the voluntary saccade returning the eye to the midline lasts three or four times longer than normal. The presence of such saccades in the second and third cases, and in experimental lesions of the abducens nucleus (Carpenter *et al.*, 1963), may be explained by the preservation of phasic inhibition which arises (*via* the giganto-cellular tegmental field) from the burst cells of the spared pontine reticular formation (ipsilateral to the lesion). The diminution of the velocity of these saccades is due to the lack of excitation of the medial rectus, an agonist for this movement. First of all it may be concluded that phasic excitation of the motoneurons of the agonist muscle is absolutely necessary for the generation of a voluntary saccade from the midline to a lateral position. Phasic excitation also plays a critical role in producing a normal velocity of a saccade which is returning toward the midline. However, when phasic excitation of the motoneurons of the agonist muscle is lacking, the return to the midline in a saccade (voluntary saccade or quick phases of nystagmus), although slower, remains possible if the phasic inhibition of the antagonist muscle neurons is preserved. Finally, when only the disfacilitation of the tonic cells of the pontine reticular formation persists and results in a voluntary return to the midline, the movement is very slow and can no longer be called a 'saccade'. In this pathological state the quick phases of vestibular or optokinetic nystagmus are also absent.

Smooth pursuit movement. Horizontal smooth pursuit movements are notoriously unstable and are often disturbed by brain lesions. Consequently, explanation of the cause of their disturbance in complex ophthalmoplegias such as the 'one-and-a-half' syndrome becomes very difficult. Since only one of our cases includes a post-mortem study, our proposals are tentative. Therefore, we shall particularly emphasize Case 1 in this discussion. Furthermore, only the foveal smooth pursuit will be considered since the full-field pursuit pathways (optokinetic nystagmus) are partially separated (Baloh, Yee and Honrubia, 1980) and, additionally, because the specific characteristics of optokinetic nystagmus are not easy to evaluate when another nystagmus such as the 'ataxic' nystagmus continually interferes.

In Case 1, the total absence of movement to the right and the right eye's lack of adduction in attempted smooth pursuit, as in lateral conjugate movement in general, are due to the damage of the right abducens nucleus and of the right medial longitudinal fasciculus. It also should be noticed that movements of the left eye within the outer hemifield of movement were markedly affected in both horizontal directions during the attempted smooth pursuit. As the left eye abducted, smooth pursuit was replaced by small and successive saccades without any abducting slow displacement. In normal subjects, when the object's velocity is high, saccades produced by the phasic cells of the pontine reticular formation replace smooth pursuit produced by the adjoining tonic cells of the pontine reticular formation. There is a somewhat variable velocity threshold for the onset of the saccades. As the velocity increases beyond the threshold the frequency and amplitude of saccades interspersed in the smooth movements became larger. For very high velocities there are only successive saccades. In pathological states the velocity threshold for the onset of the saccades decreases according to the degree of damage to the smooth pursuit system. In the extreme, even for the lowest stimulation velocities only saccades occur as in the abducting pursuit movement of the left eye of the first case. In this situation the movement is completely performed by the phasic cells of the intact pontine reticular formation, which govern all the types of ipsilaterally-directed saccades. What is the situation now for the reverse movement? The left eye returns to the midline quite slowly, but in our opinion this is probably not a true part of the smooth pursuit movement. The velocity of the returning eye (about 10 deg/s) is too slow, almost unvarying, and in a curious way mimicking the velocity of the very slow voluntary return to the midline. These observations suggest that both return movements are the result of a common process, a voluntary disfacilitation originating from the tonic cells of the intact pontine reticular formation . In the first case it is possible to conclude that all horizontal smooth pursuit movements have been abolished, even for the left eye in the outer hemifield of movement, since the smooth characteristic of the pursuit movement is absent as the eye abducts and, as the eye returns to the midline, the movement although smooth is not an actual pursuit movement.

We must not omit to consider the point that pursuit movements of the abducting eye are also saccadic in nature after a unilateral lesion of the opposite medial longitudinal fasciculus provoking internuclear ophthalmoplegia (Pierrot-Deseilligny and Chain, 1979), a syndrome which exists in the first case. However, it must be noted that although the differences between smooth pursuit disturbances in a complete internuclear ophthalmoplegia (due to lesions which barely overlap the medial longitudinal fasciculus as in Cases 3, 4 and 5) and those induced by a lesion involving almost the entire tegmentum on one side (as in Case 1) are slight, they are, nevertheless, important. Unlike the first case, in the last three cases the eye opposite the lesion abducts in a pursuit movement which includes very small, slow deflections close to the midline. In addition, in these latter cases, the same eye then returns to the midline, with a pursuit movement velocity (up to 20 deg/s) which is both more variable and faster than those in the first case. These differences support our view that in the first case the smooth pursuit by the left eye is abolished in both horizontal directions, independently of the internuclear ophthalmoplegia. The internuclear ophthalmoplegia even when complete, impairs but does not abolish pursuit movements.

These considerations raise another question: how does a large but strictly unilateral lesion of the lower pontine tegmentum abolish smooth horizontal pursuit in both directions? This question touches on the pontine course of the occipito-parieto-pontine pathways (OPPP) and the part played by the pontine reticular formation during pursuit movements. An answer can be given by comparing data from the present first case and from one reported previously (Pierrot-Deseilligny, Chain, Gray, Escourolle and Castaigne, 1979). In the latter, a relatively small and unilateral infarction of the upper pontine tegmentum abolished horizontal smooth pursuit movements, but only in the direction contralateral to the lesion. The lesion was bifocal, including both an extreme paramedian location which ended just ventral to the medial longitudinal fasciculus and another locus on the same side in the lateral pontine tegmentum. In the 1979 case it was concluded that the unilateral absence of smooth pursuit was probably due to the damage of one of the two OPPP that are crucial to horizontal pursuit. Furthermore, it was proposed that each of these pathways decussates at least once below the upper pons, yet the number of decussations and the locations of these decussations remain unknown. The preservation of smooth pursuit movements toward the side of the lesion was explained in the 1979 case by the integrity of the abducens nucleus and most of the pontine reticular formation, a principal relay for smooth pursuit as for saccades (Cohen *et al.*, 1968; Goebel *et al.*, 1971; Cohen and Komatsuzaki, 1972; Keller, 1974; Kubo *et al.*, 1978; Pierrot-Deseilligny, Chain, Gray, Escourolle and Castaigne 1979; Eckmiller and Mackeben, 1980). On the basis of this case, it was suggested that horizontal smooth pursuit movements in the brain-stem have the following organization: (a) the pontine reticular formation controls the ipsilateral smooth pursuit; (b) the OPPP involved in horizontal smooth pursuit and terminating in the pontine reticular formation decussates at least once in the lower brain-stem. Thus a unilateral lesion located at the level of the pontine reticular formation may abolish both ipsilateral smooth pursuit by the damage of this formation and contralateral smooth pursuit by the damage of the adjoining OPPP before its lower decussation (fig. 8). The present case appears to support this conception, and allows us to go further into details of the mechanisms involved.

One characteristic common to the 1979 observation and Case 1 is the saccadic feature of the pursuit movement contralateral to the lesions. The saccadic substitution for smooth movement could result from interruption of a OPPP at a point before it decussates. The lesions of the two cases also have common topographies including the lateral part of the pontine tegmentum and probably the paramedian region ventral to the medial longitudinal fasciculus. In the present first case the paramedian region was not directly damaged by the hæmorrhage, but its function was possibly affected by the ensuing œdema. For this reason the comparison of the two lesions does not provide satisfactory information about the precise location of the corticopontine fibres in the pontine tegmentum concerned with contralateral pursuit movements. However, the conservation of discrete, smooth pursuit movements contralateral to the lesion in the last two cases of our study—where the evidence suggests the lesions are mainly paramedian—leads us to propose that these fibres do pass in the lateral pontine tegmentum.

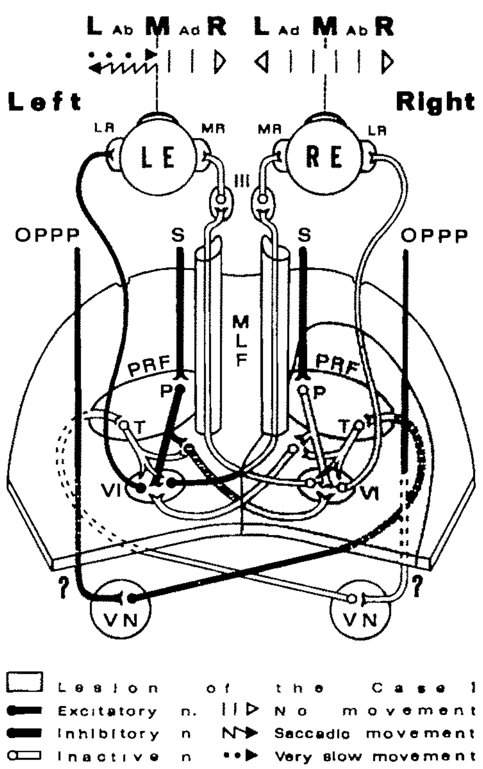

FIG. 8. *Diagram of horizontal foveal pursuit (with its hypothetical organization in the brain-stem) and of the lesion (simplified), Case 1.* Ab = abduction; Ad = adduction; L = left; LR = lateral rectus; M = midline; MLF = medial longitudinal fasciculi; MR = medial rectus; n = neuron; OPPP = occipito-parieto-pontine pathways involved in horizontal smooth pursuit movements; P = phasic cells; PRF = pontine reticular formation; R = right; S = cortico-pontine tracts involved during the horizontal saccades; T = tonic cells; VN = vestibular nuclei; III = medial rectus subdivisions of the oculomotor nuclear complex; VI = abducens nucleus. ? = each OPPP may also decussate at the level of the abducens nucleus and connect with the tonic cells (T) of the contralateral PRF, without passing through the ipsilateral vestibular nucleus.

One primary difference between the two cases clarifies the role of the pontine reticular formation in the horizontal smooth pursuit movements. In the 1979 case, the capacity for unidirectional smooth pursuit ipsilateral to the lesion was preserved, while in the present first case it was lost. At first, the two cases differ anatomically by the damage of the abducens nucleus and the medial longitudinal fasciculus in the present Case 1 but not in the 1979 case. The specific oculomotor disorders resulting from the damage of these structures have been discussed above, and we shall only consider in Case 1 the pursuit movement responsible for the return to the midline of the eye contralateral to the lesion. The two cases also differ by the integrity of most of the pontine reticular formation ipsilateral to the lesion in the one (the 1979 case) and by its damage in the other (the present Case 1). Consequently, in the present first case, we presume that the absence of pursuit movement by the left eye when returning to the midline is due to damage of the right pontine reticular formation. How can this be explained in terms of neural mechanisms controlling the opposite muscles? As previously stated, in the return of the left eye to the midline, disinhibition-excitation of the motoneurons of the agonist muscle (left medial rectus) no longer takes place since the right pontine reticular formation and abducens nucleus are damaged. Furthermore, in the same movement, we know that disfacilitation—specific to the smooth pursuit—of the motoneurons of the antagonist muscle (left lateral rectus) cannot occur because of the lesion of the right OPPP before its final decussation: given that the right OPPP mediates both the excitation of motoneurons of the left lateral rectus during the leftward smooth pursuit movement and the disfacilitation of the same motoneurons during the opposite movement. Theoretically, the only mechanism purely related to smooth pursuit available for the movement would involve an inhibitory pathway synapsing with the neurons of antagonist muscles (in the left abducens nucleus). This inhibitory pathway could arise from either an ipsilateral descending pontine pathway—which has been excluded previously (Pierrot-Deseilligny, Chain, Gray, Escourolle and Castaigne, 1979)—or from an ipsilateral ascending vestibular pathway. The extreme slowness of the left eye's return to the midline by attempted smooth pursuit—which is, as argued above, a very impaired voluntary movement resulting solely from disfacilitation of the tonic cells of the intact left pontine reticular formation—has led us to suggest that in this case inhibition did not take place. Consequently, the absence of inhibition probably results from damage to the right contralateral pontine reticular formation. Horizontal smooth pursuit movements may be controlled by the pontine reticular formation in a fashion analogous to those responsible for saccades. The excitatory pathway projects to the abducens nucleus ipsilaterally and the inhibitory one contralaterally (*via* a relay in the vicinity of the ipsilateral nucleus). No evidence supports the presence of an equivalent relay for pursuit movements in the giganto-cellular tegmental field (Hikosaka and Kawakami, 1977), but one may be located in an adjoining structure. The recent electrophysiological study of Eckmiller and Mackeben (1980) in monkeys is consistent with this theory on pursuit movements by showing that certain cells located below the abducens nucleus were active only during ipsilateral smooth pursuit.

Based on these observations and considerations we propose a theory about the physiology of the horizontal pursuit movement in the brain-stem (fig. 8). At this time several experimental studies suggest that the vestibular nuclei may be an integral portion of the pathways governing the slow phase of optokinetic nystagmus (Henn, Young and Finley, 1974; Azzena, Azzena and Marini, 1974; Waespe and Henn, 1977; Robinson, 1977; Raphan and Cohen, 1978; Waespe and Henn, 1979). The existence of such a relay is still uncertain for foveal smooth pursuit, the only type of pursuit movement discussed above (Keller and Daniels, 1975; Raphan and Cohen, 1978; Wallace, Blair and Westheimer, 1978; Baloh *et al.*, 1980). Consequently the OPPP could extend either to the ipsilateral vestibular nucleus or directly to the contralateral pontine reticular formation, without passing through the vestibular nucleus but by decussating at the level of the abducens nucleus. In any case, before reaching its final course the OPPP would probably run in the lateral part of the pontine tegmentum. If a relay exists in the vestibular nucleus, the decussation in the lower brain-stem, suggested in our previous study (Pierrot-Deseilligny, Chain, Gray, Escourolle and Castaigne, 1979), could be one of the well-known excitatory pathways that pass from each vestibular complex to the contralateral abducens nucleus. The importance of commissural fibres at this level is stressed by de Jong's observations (1980) that in the monkey midsagittal sections of the medulla and lower pons produced loss of optokinetic after-nystagmus and major impairment of horizontal optokinetic nystagmus. Finally, all excitatory pathways involved in the horizontal smooth pursuit movements require a relay in the pontine reticular formation near the abducens nucleus. Ipsilateral excitatory and contralateral inhibitory projections from each pontine reticular formation terminate in the two abducens nuclei. An arrangement of this kind would explain how a strictly unilateral lesion of the lower pontine tegmentum can completely abolish bidirectional horizontal smooth pursuit movements. Damage to one pontine reticular formation in the paramedian tegmentum eliminates the ipsilateral smooth pursuit movement, and interruption in the adjoining lateral tegmentum of the ipsilateral OPPP, before its final decussation to the contralateral pontine reticular formation, abolishes the contralateral smooth pursuit movement.

Oculocephalic movements. At present, the circuitry for oculocephalic movements is not clearly known. The findings from our five cases do provide insights that we can use to form hypotheses about the physiology underlying such movements. Three types of afferent pathways are involved in the reflex oculocephalic movement evoked in our study (Meiry, 1971): a visual pathway related to fixation, a proprioceptive pathway arising from the muscular and vertebral structures of the neck (since the head is rotated on a fixed trunk), and a vestibular pathway which is particularly important with rapid displacements of the head. To reiterate, the visual and the proprioceptive (Frederickson, Schwarz and Kornhuber, 1965) inputs probably pass by way of the vestibular nuclei. The vestibular afferent signals are functionally the most important (Takemori and Suzuki, 1971; Dichgans, Bizzi, Morasso and Tagliasco, 1974). So it seems reasonable to consider the efferent pathways for oculocephalic movements as arising from the vestibular nuclei.

The generally accepted arrangement has each vestibular complex projecting excitatory connections to the oculomotor nuclei controlling contralateral movements and an inhibitory pathway to the oculomotor nuclei responsible for the ipsilateral movements (Carpenter, 1971; Cohen, 1971; Precht, 1977). There are three distinct excitatory pathways. The first (fig. 9, pathway A-A′), which probably passes through the medial longitudinal fasciculus (Precht, 1977), includes only one neuron between the vestibular nucleus and the contralateral abducens nucleus. The pathway reaches the abducens nucleus motoneurons and the internuclear neurons that excite the medial rectus motoneurons (Baker and Highstein, 1975; Nakao and

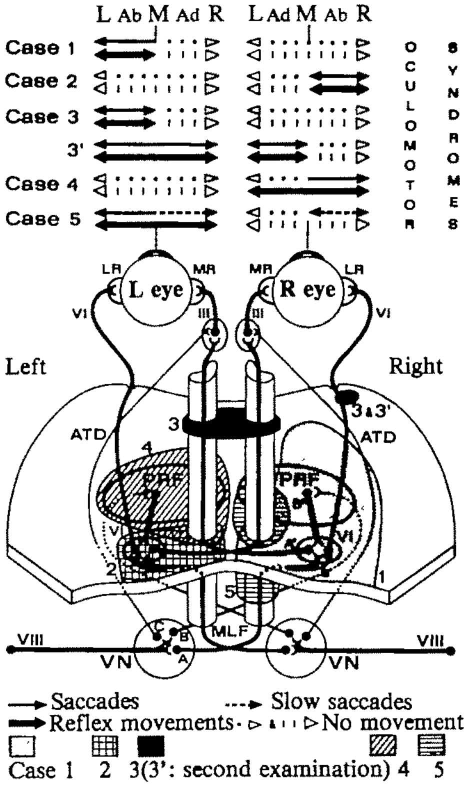

FIG. 9. *Main oculomotor characteristics and simplified (Case 1) or assumed (Cases 2, 3, 4 and 5) lesions of the five 'one-and-a-half' syndromes* A = pathway between the vestibular nucleus and the contralateral abducens nucleus; Aa = pathway linking the vestibular nucleus and the motoneurons of the contralateral abducens nucleus; A′ = excitatory internuclear neurons of the abducens nucleus; B = pathway connecting the vestibular nucleus and the contralateral PRF; B′ = pathway connecting the PRF and the abducens nucleus; C = ATD, connecting the vestibular nucleus and the ipsilateral medial rectus motoneurons. Ab = abduction; Ad = adduction; ATD = ascendant tract of Deiters; L = left; LR = lateral rectus; M = midline; MR = medial rectus; MLF = medial longitudinal fasciculus; PRF = pontine reticular formation; R = right; III = medial rectus subdivision of the oculomotor nuclear complex; VI = abducens nucleus and nerve; VIII = vestibular nerve.

Sasaki, 1978). The second (fig. 9, pathway B-B′-A′) passes to the contralateral pontine reticular formation and from there to the dorsally-located abducens nucleus (Lorente de Nó, 1933; Szentágothai, 1950; Gernandt, 1964; Cohen, 1971; Peterson and Abzug, 1975; Highstein *et al.*, 1976; Hikosaka, Maeda, Nakao, Shimazu and Shinoda, 1977; Kubo *et al.*, 1978). The third (fig. 9, pathway C) is the ascending tract of Deiters described in the cat. Passing in the dorsal part of the pontine tegmentum between the medial longitudinal fasciculus and the brachium conjunctivum, Deiters' ascending tract is a monosynaptic pathway between the vestibular complex and ipsilateral medial rectus motoneurons (Gacek, 1971; Baker and Highstein, 1978). According to Reisine and Highstein (1979) this third pathway only mediates excitation elicited by head rotation. It is possible that an equivalent pathway terminates on the motoneurons of abducens nucleus (fig. 9, pathway A-a).

It is generally accepted that an inhibitory pathway unites the vestibular complex with the ipsilateral abducens nucleus; however, at the present time, a similar inhibitory pathway to the medial rectus motoneurons is questioned (Baker and Highstein, 1978; Uchino *et al.*, 1979).

The deficits in reflex movements in the cases of this report may be explained by this organization. To review, a lesion of the medial longitudinal fasciculus located rostral to the abducens nucleus suppresses adduction during all versional movements of the ipsilateral eye (Pierrot-Deseilligny and Chain, 1979) and in our cases the fixed eye could not adduct. These facts suggest that it is principally the excitatory internuclear neurons of the medial longitudinal fasciculus—arising from the contralateral abducens nucleus and receiving afferent input by the pathways A-A′ and B-B′-A′—that are involved in the oculocephalic movement; consequently, Deiters' ascending tract alone (pathway C) cannot mediate this movement. The same pathways (A-A′ and B-B′-A′) control excitation of the agonist muscles for lateral gaze. They are damaged in the three first cases accounting for the lack of both abduction of the fixed eye and adduction of the opposite eye during reflex movements ipsilateral to the lesion. In the fourth case, since adduction of the right eye by the oculocephalic movement is conserved and abduction is absent in the left (fixed) eye, two different interpretations are possible. Adduction of the right eye during the oculocephalic movement could theoretically be executed by ipsilateral uncrossed excitatory tracts (passing, for instance, in the right medial longitudinal fasciculus and Deiters' ascending tract), with a contralateral lesion possibly damaging the left abducens nucleus. Alternatively, the left abducens nucleus is preserved and excitatory internuclear neurons ascending from it in the right medial longitudinal fasciculus mediate the leftward oculocephalic movement of the right eye. The latter interpretation is favoured by the data from our observations. In our present first case, as in the case of Fisher (1967) and Masson *et al.* (1978), after unilateral lesions damaging the abducens nucleus, oculocephalic movements were abolished in the opposite adducting eye. On the other hand, in the first case of an earlier clinicopathological study (Pierrot-Deseilligny, Chain, Gray, Escourolle and Castaigne, 1979), the movements elicited just as described above, which were directed toward the side of the lesion, were preserved for the opposite adducting eye but not for the ipsilateral abducting eye; the causative lesion involved both the pontine reticular formation and the abducens motoneuron fibres, but not the nucleus itself.

Lastly, in our fifth case, the right abducens nucleus and its root fibres were certainly intact since voluntary right lateral gaze was largely retained in both eyes. However, the horizontal oculocephalic movements of the two eyes differed. The movement appeared normal for the left eye which travelled through the entire range of ocular movement, while it was almost abolished for the right eye which barely abducted. As in the fourth case, the preserved oculocephalic movement for the eye opposite the lesion was probably due to the integrity of the excitatory internuclear neurons originating in the undamaged abducens nucleus ipsilateral to the lesion.

Damage of the medial longitudinal fasciculus at the level of, or just rostral to, this abducens nucleus, which interrupted the fibres of excitatory internuclear neurons arising from the opposite abducens nucleus, accounted for the inability of the eye ipsilateral to the lesion to adduct. In addition, this same lesion could extend caudal to the abducens nucleus and at that level also involve the medial longitudinal fasciculus, thus interrupting the main afferent reflex pathways to the abducens nucleus and abolishing abduction of the same eye during oculocephalic movements. Since the abducens nucleus motoneurons and the excitatory internuclear neurons are scattered throughout the abducens nucleus, how can the eye opposite the lesion adduct while the ipsilateral eye does not abduct during the oculocephalic movement? This probably is explained by a hierarchy in the different excitatory reflex pathways. In other words, pathway A would convey the primary input and the pathways A-a and B-B′ would convey accessory inputs for the lateral rectus motoneurons. Conversely, the pathway A-A′ would convey the primary input and the pathways B-B′-A′ and C would convey accessory inputs for the medial rectus motoneurons. The preservation of only the accessory pathway B-B′ for the right lateral rectus motoneurons accounts for the very slight abduction of the right eye; the conservation of two accessory pathways (B-B′-A′ and C) to the left medial rectus motoneurons explains the adequate adduction of the left eye. This hypothesis supports the idea that Deiters' ascending tract mediates certain oculomotor impulses (Reisine and Highstein, 1979), but alone is inadequate for adduction. Although a secondary system, this tract could provide the crucial linkage in special instances such as our fifth case.

SUMMARY

The 'one-and-a-half' syndrome combines a lateral gaze palsy in one direction with an internuclear ophthalmoplegia in the other direction. In the complete form of the syndrome, one eye lies fixed at the midline for all lateral movements, while the other eye can only abduct and exhibits an ataxic nystagmus in abduction. Since this syndrome is usually produced by a single unilateral lesion of the dorsal part of the lower pontine tegmentum, it is not uncommon. The structures damaged in this syndrome are those that mediate ipsilateral conjugate gaze, and the medial longitudinal fasciculus which controls adduction of the ipsilateral eye. We report the first electro-oculographic analysis of this syndrome in five cases, in one of which pathological examination was performed.

Four main theoretical variations of the 'one-and-a-half' syndrome are illustrated in our cases. They relate to different topographical locations of the lesions and to distinctive features of the deficiencies of lateral gaze. The lateral gaze palsy may be produced by damage to both the pontine reticular formation and abducens nucleus (Case 1); to the abducens nucleus only (Case 2); to both the root fibres of abducens nucleus and the contralateral medial lateral fasciculus when two lesions are

involved (Case 3); and to the pontine reticular formation only (Case 4). Two clinical features allow us to differentiate between the syndrome produced by damage to a single abducens nucleus (Case 2) and that produced by damage solely to the ipsilateral pontine reticular formation (Case 4): (a) the preservation of ipsilateral saccades within the hemifield of movement contralateral to the lesion in the former (but not in the latter); (b) the preservation of oculocephalic movements within the hemifield of movement ipsilateral to the lesion in the latter situation (but not in the former). With lesions of both the abducens nucleus and the pontine reticular formation, disorders (a) and (b) are both present (Case 1). Clinical differentiation is also possible between cases with damage to both the root fibres of the abducens nucleus and the contralateral medial longitudinal fasciculus by two separate lesions (Case 3), and cases involving only a damaged abducens nucleus. A lateral gaze palsy which is clearly not conjugate at any time during its evolution supports the existence of two lesions, while a constantly conjugate palsy is in favour of damage to the abducens nucleus.

Certain explanations or hypotheses are put forward in an attempt to describe the organization of the different lateral movements in the brain-stem. Normal voluntary saccades are presumed to result from the action of phasic excitation involving the motoneurons of the agonist muscles and from the action of phasic inhibition that involves the motoneurons controlling the antagonist muscles. It appears first that phasic excitation is indispensable for the eye to traverse the midline to a lateral position during a saccade, and that this action plays a major part in causing the return movement to the midline at a normal velocity. If, however, this phasic excitation is suppressed, the presence of intact connections for phasic inhibition is responsible for a slow saccade returning to the midline. If, in addition, phasic inhibition is absent, there can be a very slow voluntary return to the midline which is no longer a 'saccade'. Hypothetically, the intrinsic organization of the brain-stem which is necessary for the horizontal foveal pursuit movements, as well as for the saccades, would include an excitatory pathway arising from each pontine reticular formation and projecting to the ipsilateral abducens nucleus, and an inhibitory pathway arising from each pontine reticular formation and projecting to the contralateral abducens nucleus. The pontine reticular formation is the last relay in the occipito-parieto-pontine pathways mediating the horizontal foveal pursuit movements. Before reaching the pontine reticular formation these descending pathways may run in the lateral part of the pontine tegmentum and decussate in the lower brain-stem after a possible relay in the vestibular nucleus. Finally, the functional importance of three excitatory reflex pathways is proposed and discussed. These excitatory reflex connections appear to pass from one vestibular complex to the two oculomotor nuclei involved in the contralateral conjugate gaze. The first of these pathways projects to the contralateral abducens nucleus monosynaptically. The second passes to the contralateral pontine reticular formation and the abducens nucleus. The third, the ascending tract of Deiters, terminates on the ipsilateral medial rectus motoneurons.

ACKNOWLEDGEMENTS

The authors wish to acknowledge their gratitude to Miss Trish Perl for the English translation of the manuscript and to Mrs Christiane Penet for her technical assistance. This work was performed in the Research Unit INSERM U.84.

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(*Received March 3, 1981*)

Brain (1981) **104**, 701-719

FACILITATION OF MONOSYNAPTIC REFLEXES BY VOLUNTARY CONTRACTION OF MUSCLES IN REMOTE PARTS OF THE BODY

MECHANISMS INVOLVED IN THE JENDRASSIK MANŒUVRE

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INTRODUCTION

It has long been known that voluntary contraction of muscles in the upper limb increases the amplitude of tendon reflexes in the lower limb; this is the classical Jendrassik (1885) manœuvre. It has since been shown that the remote facilitation is exerted equally on flexor and extensor motoneurons, and also that the amplitude of upper limb reflexes is increased following voluntary contraction of muscles in the lower limb (Delwaide and Toulouse, 1980; Toulouse and Delwaide, 1980).

The factors responsible for this facilitation are poorly understood, and there has been for some time a controversy concerning the elements of the myotatic reflex arc which may be involved. Some authors (Hagbarth, Wallin, Burke and Löfstedt, 1975; Bussel, Morin and Pierrot-Deseilligny, 1978) believe that only alpha motoneurons are facilitated, while others (Burg, Szumski, Struppler and Velho, 1974) hold that gamma motoneurons are also excited. But no study has been made of those characteristics of the conditioning contraction which determine the increase in amplitude of remote monosynaptic reflexes, nor of the nervous structures and circuits which are concerned in the transmission of the facilitatory influences to motor nuclei. Undoubtedly many have been deterred by the complexity of the classical Jendrassik conditioning manœuvre, which is ill standardized and brings in sequentially a large number of muscles which develop forces and movements which are difficult to control experimentally.

In order to isolate the effective factors of the conditioning contraction, we suggested replacing the classical Jendrassik manœuvre by a selective contraction of the wrist extensors. This simplified procedure turns out to be as effective as the classical manœuvre, and permits measurement of the various parameters of the conditioning contraction, which can be modified on demand and reproduced at will.

Facilitation obtained by this method may be quantified and reproduced after identical conditioning procedures. We have been able to show that the amplitude of a reflex in a leg muscle varies as a function of the time separating it from the command to contract. When the subject makes a rapid extension of the wrist followed by maintenance of the new position, the curve of facilitation is complex; in it can be distinguished three phases based on the intensity of facilitation and the latency of its onset (Delwaide and Toulouse, 1980). The question then arises as to whether these phases are due to variations in the effectiveness of a single mechanism, or whether they derive from separate facilitatory processes. Previous results appear to favour the second alternative: during phase II the H-reflex of soleus is facilitated to the same extent as a tendon reflex of the same amplitude, while during phase III the H-reflex is no longer facilitated while the tendon reflex is. However, further research appears to be necessary.

The present investigation attempts, first, to define those factors in the conditioning contraction which determine the amplitude of the testing monosynaptic reflex during the different phases, and, second, to identify the neural structures involved in the transmission of facilitation to the distant motor nuclei. To achieve these objectives, we have systematically modified the conditioning contraction: first, by increasing its strength, next by changing its speed and duration in ballistic movements and slowly increasing contractions. We have also dissociated the will to contract from the electromyographic activity of the conditioning muscles by recording the responses to attempts at contraction in paralysed subjects and, conversely, by eliciting a tonic vibration reflex (TVR) in the wrist extensors. Pursuing this latter line, designed to explore the role of proprioceptive muscle afferents, we have also investigated the effect of passive stretch of the conditioning muscles. These experiments have shown that it is possible to isolate the different phases of the remote facilitation and that each is determined by separable factors.

Next we have investigated the generators of the various facilitatory effects and the circuits by which they reach the distant motor nuclei. To this end, we have compared the effects brought about by identical conditioning contractions ipsi- and contralateral to the testing reflex. Finally, we have measured the latencies of the various phases in two motor nuclei, one lumbar, the other cranial, following voluntary contraction of a muscle group in the leg. This experiment made it possible to identify the sequence of facilitations in two motor nuclei several tens of centimetres apart.

SUBJECTS AND METHODS

Investigations were carried out on neurologically healthy volunteers and on a number of selected neurological patients. There were 27 volunteers of both sexes, aged between 17 and 35 years (mean 23). They did not all undergo all the tests described herein; some were studied several times. The number used in each experiment is indicated in the section on Results. Their informed consent was obtained.

Eight male patients with complete unilateral radial paralysis, aged between 18 and 52 years (mean 37), were also studied. In 5 cases, the lesion was due to compression in the upper arm and in the other 3 to fracture of the humerus.

The subjects were seated in a special chair designed for the study of reflexes (Delwaide, 1971), in which it was possible to immobilize the lower limbs. The angles between the foot and tibia and between the lower leg and femur were fixed at 110 to 120 deg and 110 to 130 deg, respectively. The forearms reposed on armrests. In addition, if required by the experimental protocol, the forearm and hand on one side could be fixed so that isometric contractions could be performed. The slightly extended head was supported by a headrest. The eyes were open and the subjects were in a room with constant temperature and low lighting. All examinations were carried out in silence. The subjects had their backs to the experimenters and to the recording equipment, with the exception of a storage oscilloscope on which the subjects could see the tracings of conditioning contractions (*see below*).

Earlier experiments had shown that a given conditioning contraction facilitated the tendon reflex of the quadriceps to a greater extent than that of soleus (Toulouse and Delwaide, 1980). Thenceforward the quadriceps tendon reflex, since it appeared to be the most sensitive, was chosen for testing the effects of the parameters of the conditioning contraction.

The quadriceps tendon reflex was elicited by single and identical taps delivered by a Bruel and Kjaer No. 4809 vibrator solidly fixed in front of the patellar tendon. The hammer was in contact with the skin. The percussion was set off by an electrical signal from a Bruel and Kjaer No. 2706 power supply. The tap was always orientated so as to elicit the most ample possible reflex response.

The masseter tendon reflex was elicited by percussion delivered by a Bruel and Kjaer No. 4810 vibrator solidly fixed in contact with the point of the chin and activated by the same power supply. The upper and lower teeth were occluded but not clenched. Despite the constancy of the percussion, the reflex responses fluctuated in amplitude, in agreement with the observations of Lewis, Pilcher and Yemm (1980).

Reflex activity was recorded by cutaneous electrodes (Disa No. 13K60) fixed, for the quadriceps reflex, on the tendon of rectus femoris 3 cm above the patella and 1.5 cm proximal to this over the muscle belly; and, for the masseteric reflex, on the insertion of the masseter tendon into the mandible and 1.5 cm higher up on the muscle belly.

Potentials were amplified by a plug-in Tektronix 3A9 unit and visualized on the screen of a Tektronix 565 oscilloscope. The bandpass allowed through frequencies between 0.1 Hz and 1.0 mHz. Potentials were subsequently measured peak-to-peak by a Tektronix 230 digital unit, and numerical values transcribed by a Hewlett Packard printer. Photographs were occasionally taken by an Alvar Cathomatic camera.

Every 10 s a Devices Digitimer D4030 triggered the following sequence:

(a) a low-intensity sound lasting 3 s gave the command to the subjects to carry out, as soon as possible, the procedures indicated by the experimenter (*see below*);
(b) percussion of tendons after regulable delays;
(c) oscilloscope sweeps.

Time 0 was taken at the beginning of the Digitimer cycle. The quadriceps or masseteric reflexes were elicited at variable delays, every 50 ms during the first 300 ms, then at 400, 700, 1000, 1500, and 2500 ms. When it was desired to study more closely certain critical points on the curves such as the beginning or the peak of the phases, 10 ms intervals were used. At least 20 responses were measured at every interval without any conditioning, and their mean taken as reference. The low-intensity sound signal did not induce modification of reflexes.

When the sound signal gave the command to carry out a conditioning contraction (*see below*), 20 reflex responses were elicited at the same delays as above. The variations in amplitude of the quadriceps and masseteric reflexes expressed as a percentage of reference values were plotted as ordinates, the delays as abscissæ.

The tendon reflexes were conditioned in several ways:

1. By voluntary contraction, as selective as possible, of the ipsi- or contralateral wrist extensors, or of the foot dorsiflexors contralateral to the lower limb under test. EMG activity of the conditioning contraction was recorded on a Siemens mingograph; electrodes over synergist and antagonist muscles

verified the selectivity of contraction. Some contractions were carried out under isometric conditions, and a strain gauge (Grass 7940) fixed to the dorsum of hand or foot measured the tension developed. The recording of these events (No. 3C66 plug-in Tektronix) was visualized by a 564B storage oscilloscope placed in front of the subject, who could thus reproduce identical contractions (tension; rate of rise; duration).

The subjects were asked, after a practice period, to carry out:

(a) a contraction rising rapidly (> 100 to 200 ms) to a certain tension and then to be maintained at the same tension throughout the duration of the sound signal. Different levels of tension have been reached at the same rate;

(b) a slowly rising contraction to reach the same tensions as the above by the end of the 3-s sound signal;

(c) a very brief isotonic ballistic contraction with EMG activity lasting 200 ms, without control by the strain gauge.

The eight patients with radial palsy were signalled to try to carry out rapidly-reached maintained contractions like those performed in 1a.

Complementarily to this, one of the investigators (P.J.D.) tried to perform rapidly-reached maintained contractions, before and during local blocking of the posterior branch of the radial nerve with 10 ml of 1 per cent xylocaine.

2. By a vibratory stimulus applied to the wrist extensors by a Keydon TMT 18 vibrator (100 Hz for 3 s, amplitude 1 mm). The onset of the vibratory stimulus triggered the Devices Digitimer at time 0 in relation to which the quadriceps tendon reflex was timed; the upper limb hung down by the side. The occurrence of a tonic vibration reflex was noted.

3. By passive stretching of the wrist extensors. In this case, a Sansui helmet transmitted a sound signal to the experimenter. On hearing it, the experimenter pulled as rapidly as possible on the wrist extensors, briefly and sharply flexing the joint. A Bruel and Kjaer (type 4343) accelerometer, placed on the back of the hand, made it possible to time the moment of displacement in relation to the beginning of the sound signal at time 0.

4. Finally, the quadriceps and masseter tendon reflexes were conditioned by contraction of the foot dorsiflexors on the side contralateral to the quadriceps tendon reflex under test. This contraction rose rapidly and was then maintained until the end of the sound signal. The start of the EMG in tibialis anterior constituted time 0 in relation to which the reflex was timed.

Necessary precautions were taken during study of the Jendrassik manœuvre (Hagbarth *et al.*, 1975; Delwaide and Toulouse, 1980). In particular, care was taken to see that the various conditioning procedures did not evoke any EMG activity in quadriceps. If such activity was seen, that test was discarded.

RESULTS

A. *Modifications in the Parameters of the Conditioning Contraction and Investigation of the Factors Influencing Facilitation*

1. *Influence of the intensity of conditioning contraction* (*12 subjects*). Fig. 1 shows the results obtained in one experiment. In A, facilitation of the quadriceps tendon reflex is plotted as a function of the delay. Each curve corresponds to a different intensity of the conditioning contraction of the wrist extensors. Fig. 1B details the evolution of reflex amplitude during the first 150 ms after the beginning of the command to contract. The four curves, in both A and B, exhibit common characteristics. First, after a delay of about 70 to 80 ms there is progressive

facilitation which is more marked the more intense the conditioning contraction. This facilitation appears before electromyographic activity in the conditioning muscles, which appears only after 150 to 180 ms. It constitutes what we have called phase I (Delwaide and Toulouse, 1980). Then, after a delay of about 200 ms (fig. 1A), the initial facilitation suddenly becomes much more marked and attains its maximum after a latency of about 300 ms; it then decreases regularly until about 600 ms. This is phase II (fig. 1A). After about 700 ms, there is a facilitation which is less marked than that of phase II, but more stable. This phase III persists until the end of the conditioning contraction.

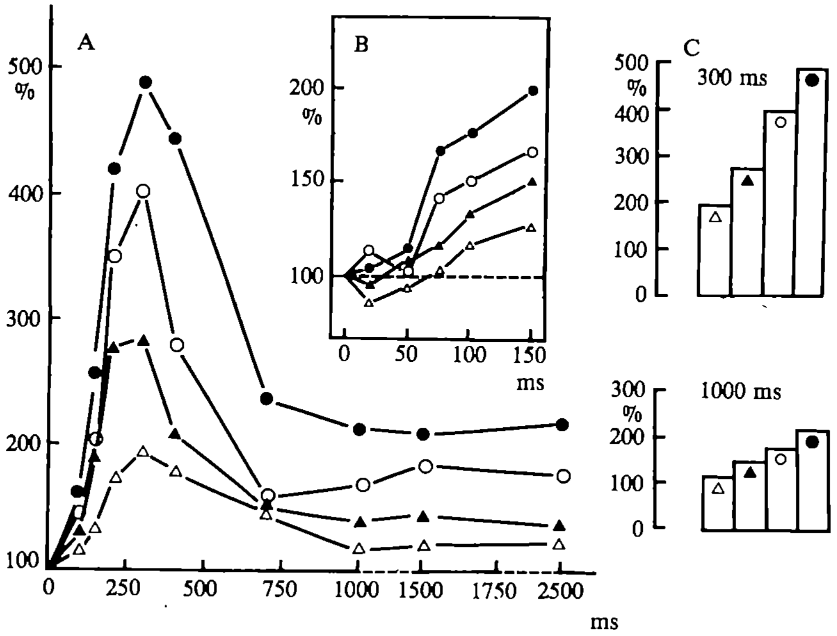

FIG. 1. Facilitation of the quadriceps tendon reflex, expressed as a percentage of control values (ordinates) following contraction of the ipsilateral wrist extensors. Abscissæ: delays between auditory command to contract and elicitation of tendon reflexes. Effects of four different intensities of conditioning contraction were studied: ●, maximal intensity; ○, three-quarters-maximal; ▲, half-maximal; △, quarter-maximal. A, curve displays phases II (from 150 to 750 ms) and III (from 700 ms onward). B, curves illustrate the facilitation of phase I. In both A and B, the facilitation is more marked as the conditioning contraction is more intense. C, facilitation at 300 and 1000 ms expressed as a function of the intensity of the conditioning contraction (● ○ ▲ △). During phase II, the intensity of the conditioning contraction has a stronger influence on the facilitation than during phase III.

The more intense the conditioning contraction, the greater the degree of facilitation. The latency of onset and the duration of the different phases, on the other hand, are not changed. The differences in facilitation, minor in phase I, are more marked in phases II and III (fig. 1A). The increase in reflex amplitude as a function of the intensity of the conditioning contraction is not uniform during the different phases. As shown in fig. 1C, the increase in amplitude is more marked after 300 ms (phase II) than after 1000 ms (phase III). During phases II and III, facilitation increases linearly with the intensity of the conditioning contraction, but with two separate slopes.

In all 12 subjects, the variation of reflex facilitation with intensity of conditioning was evident, but in four of them the differences were not seen in phase III.

2. *Types of conditioning contraction* (*9 subjects*). Current neurophysiology distinguishes pre-programmed ballistic movements of brief duration from continuously-controlled ramp movements (Kornhuber, 1971; Desmedt and Godaux, 1978). In our earlier work (Delwaide and Toulouse, 1980; Toulouse and Delwaide, 1980), the conditioning contraction used, although simplified relative to the classical Jendrassik manœuvre, appears complex—ballistic at first, then later more like a continuously-controlled contraction.

We have here separated the two types of movement; in some experiments we have restricted the conditioning contraction to the ballistic component (fig. 2A), with the

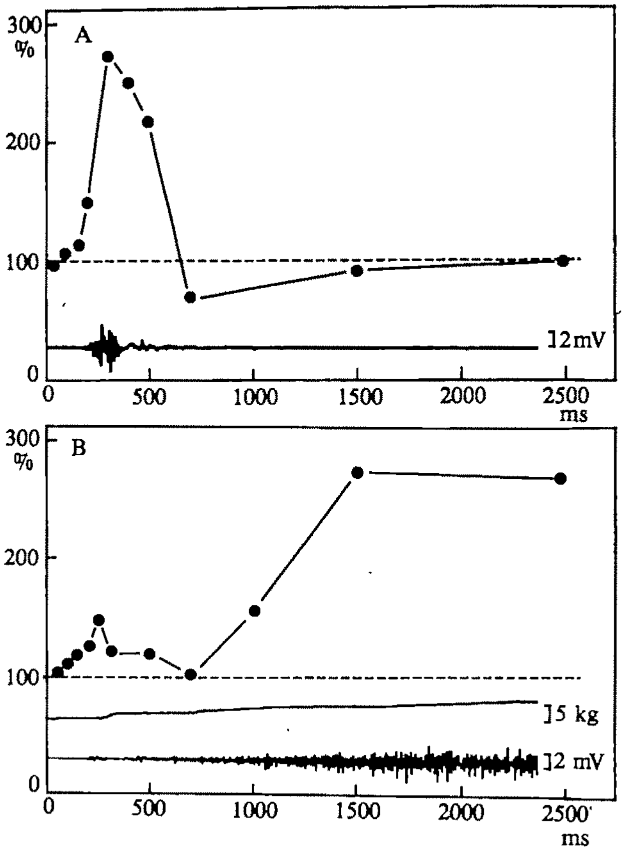

FIG. 2. Comparison of facilitations of quadriceps reflex (ordinates: percentages of control values; abscissæ: delays between command to contract and elicitation of reflexes) in A, ballistic conditioning contractions, and B, slowly progressive contractions. Electromyogram corresponding to each type of contraction, represented below each graph. Also, below, B, mechanogram of increasing strength of conditioning contraction.

subject carrying out an unopposed extension of the wrist (isotonic contraction). In other experiments, we have studied the effects of a regularly progressive conditioning contraction which was performed under isometric conditions; the progress of the contraction is illustrated in the mechanogram (fig. 2B). The results shown in fig. 2 were obtained during the same experimental session. In A, electro-myographic activity commences 180 ms after the beginning of the sound signal; it consists of a high-amplitude burst which rapidly diminishes and which lasts in all 100 to 120 ms; a moderate facilitation of the quadriceps reflex is visible from 100 ms after the onset of the sound signal. It increases rapidly after the appearance of the EMG, attaining its maximum (275 per cent in the case illustrated) after 300 ms; and is then reduced progressively up to 600 ms. After this interval, the amplitude is a little smaller than that of controls. It can be seen that the duration of facilitation clearly outlasts the electromyographic activity. Fig. 2B illustrates the facilitation brought about by progressively increasing contraction of the forearm muscles. Electromyographic activity again comes on after an interval of about 180 ms. It develops in a regular manner, causing a progressive pull on the strain gauge. The quadriceps tendon reflex is clearly facilitated from before the appearance of the electromyogram. The facilitation remains moderate until about 1000 ms; it then increases regularly until it attains, at the end of the contraction, the same level as in fig. 2A (i.e. 275 per cent). The curves in fig. 2 do not, then, lend themselves to a description involving three successive phases.

In the 9 subjects who carried out both types of conditioning contraction, the same results were observed as in fig. 2.

In fig. 3, the quadriceps reflex is conditioned by isometric contraction of the wrist extensors, the strain gauge being fixed to the back of the hand. The curves *a* and *b* are the mean of 6 experiments carried out in different subjects. Curve *a* plots the changing amplitude of the quadriceps reflex following a conditioning contraction whose EMG lasted about 200 ms. Curve *b* corresponds to differing conditioning

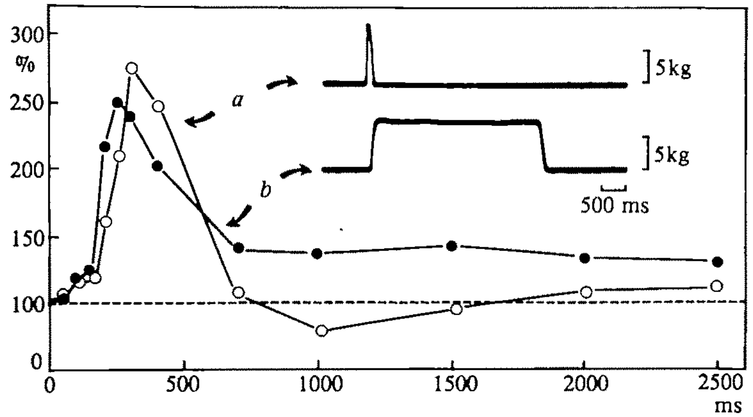

FIG. 3. Facilitation of quadriceps reflex (axes as in figs. 1 and 2) by *a*, brief contraction or *b*, a 3 s contraction of the wrist extensors. *Inset*: corresponding strain gauge records.

contractions: after reaching the same mechanogram levels as in *a* after the same delays, the subjects maintained the contraction under visual monitoring until the end of the third second, as in the experiment of fig. 1. Fig. 3 shows that facilitation is essentially similar in curves *a* and *b* for the first two phases. The differences appear after 600 ms., that is at the delay which corresponds to the beginning of phase III. The initial facilitation due to the brief contractions is followed by inhibition of the amplitude of the quadriceps reflex, while the maintained contractions are followed by a stable facilitation of about 40 per cent relative to control values.

3. *Dissociation between voluntary command and EMG activity of conditioning muscles.* Two distinct types of conditioning have been carried out:

(a) Attempts at voluntary contraction without actual muscle contraction.

When the central command is intact, voluntary contraction of wrist extensors fails in:

(i) patients with radial nerve paralysis (8 subjects). Fig. 4A illustrates what happens to the amplitude of the quadriceps reflex in such a case. Contraction

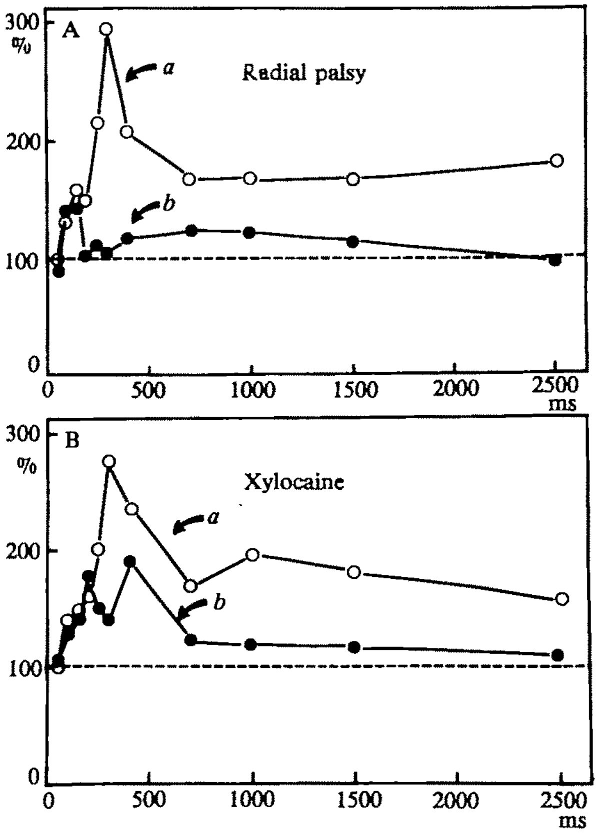

FIG. 4. A, facilitation of quadriceps reflex, *a*, after contraction of extensor muscles of the contralateral wrist or *b*, after attempted voluntary contraction of paralysed ipsilateral wrist extensors. B, facilitation of quadriceps reflex in normal subject *a* before and *b*, during blocking of radial nerve by xylocaine.

of the wrist extensors on the normal side brings about a facilitation similar in all respects to that observed in control subjects (curve *a*). Attempts at maximal voluntary contraction on the paralysed side bring about a small facilitation (curve *b*). The increase in amplitude of the quadriceps reflex begins in this case at the same latency as phase I. However, it remains of moderate extent throughout the period during which the attempt at contraction is maintained; the peak of facilitation corresponding to phase II and the phase III facilitation do not appear. The facilitation which is apparent until 1000 ms does not exceed that which is seen in phase I.

(ii) a normal volunteer with a radial nerve blocked by local anaesthetic. Fig. 4B compares the effects of voluntary command of the wrist extensors before (curve *a*) and during (curve *b*) blocking of the nerve. The latter causes a marked reduction of the attempted maximal contraction, but does not completely abolish it. During block, the facilitation is clearly reduced, but is not abolished.

Comparison of curves *a* and *b* in fig. 4 indicates that the facilitations are similar in phase I, while there are clear differences in phases II and III. These results suggest that facilitation in phase I is independent of muscle contraction, but that contraction is necessary for the appearance of phases II and III.

(b) Elicitation of continuous reflex electromyographic activity in the wrist extensors by percutaneous vibration of their tendons (7 subjects). Fig. 5 illustrates the changes in amplitude of the quadriceps reflex after applying a vibratory stimulus to the wrist extensors. Time 0 corresponds to the moment at which the vibrator is activated. Facilitation of the quadriceps reflex appears at 70 to 100 ms; it is moderate, and does not exceed 35 per cent of control values though in other cases, a facilitation of 50 per cent was seen.

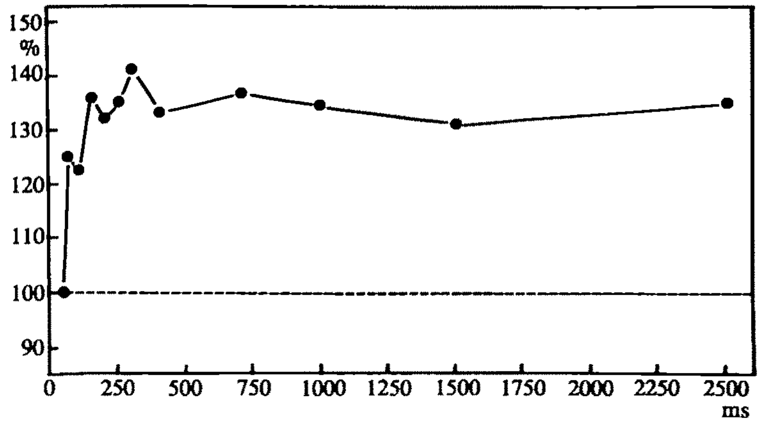

FIG. 5. Facilitation of quadriceps reflex following vibration of extensor muscles of ipsilateral wrist. Time 0 corresponds to start of vibration.

Once the facilitation is under way, it remains as a plateau until the end of the vibratory stimulus. In 5 subjects, the vibrator elicited a tonic vibration reflex in the subjacent muscles. No relationship between this reflex and the course or intensity of the facilitation was observed.

4. *Passive movement of the wrist* (*15 subjects*). Brief and rapid stretching of the wrist extensors facilitates the quadriceps reflex, as shown in fig. 6. The beginning of the movement is indicated by deflection of the accelerometer (arrow). About 70 ms later there is a rapid increase in the reflex amplitude. The facilitation develops linearly, and reaches its maximum about 150 ms after the beginning of the lengthening, after which the amplitude returns to control values. In general, the intensity of facilitation is less marked than when conditioning is brought about by voluntary contraction of the wrist extensors.

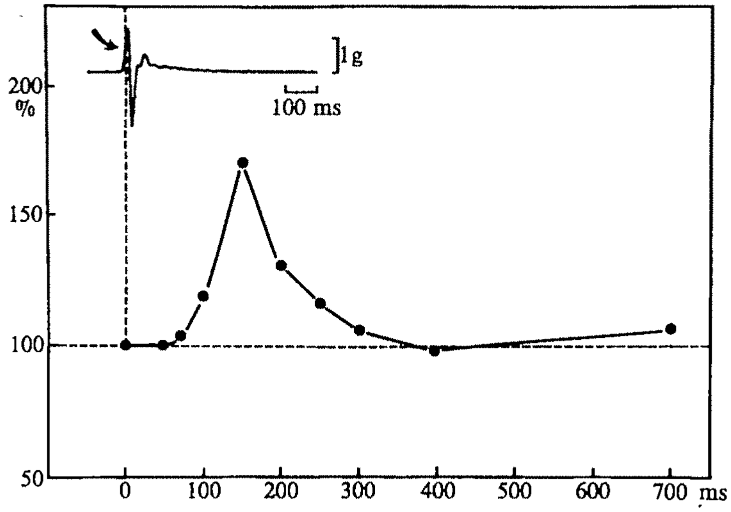

FIG. 6. Facilitation of quadriceps reflex after passively stretching wrist muscles ipsilaterally. *Above*, recording of one movement by accelerometer fixed to back of hand. Time 0 corresponds to beginning of wrist movement.

B. *Transmission of Facilitation*

1. *Comparison of the effects induced by contractions ipsi- and contralateral to the test reflex.* The quadriceps reflex is facilitated to the same extent by identical conditioning contractions on the same or on the opposite side. The three phases have the same duration and amplitude.

2. *Time course of facilitation of masseteric and quadriceps reflexes induced by conditioning contractions in the lower limbs.* We have previously shown that voluntary contraction of tibialis anterior facilitates the biceps brachii tendon reflex (Toulouse and Delwaide, 1980). Isometric contraction of the muscles of the anterior

compartment of the leg (rapid onset, then maintenance for more than 2 s) also facilitates the masseteric tendon reflex (fig. 7). Facilitation plotted against time shows three phases similar to those in fig. 1 (figs. 7A and B). Remote muscle contraction thus increases the amplitude of tendon reflexes in the caudo-rostral as well as in the rostro-caudal direction. Contraction of the anterior tibial muscles also facilitates the quadriceps reflex of the opposite leg in the usual three phases (figs. 7A and B).

The same conditioning contraction thus facilitates two motor nuclei, one situated in the brain-stem, the other in the lumbar cord. It is possible, by measuring the latencies of the various phases of facilitation in these widely separated motor nuclei, to trace the spread of the activity which is responsible for the increase in reflex amplitude. Since the spread of facilitation is a central nervous process, account must be taken of the different latency of the test reflexes: masseter 9 ms; quadriceps 23 ms.

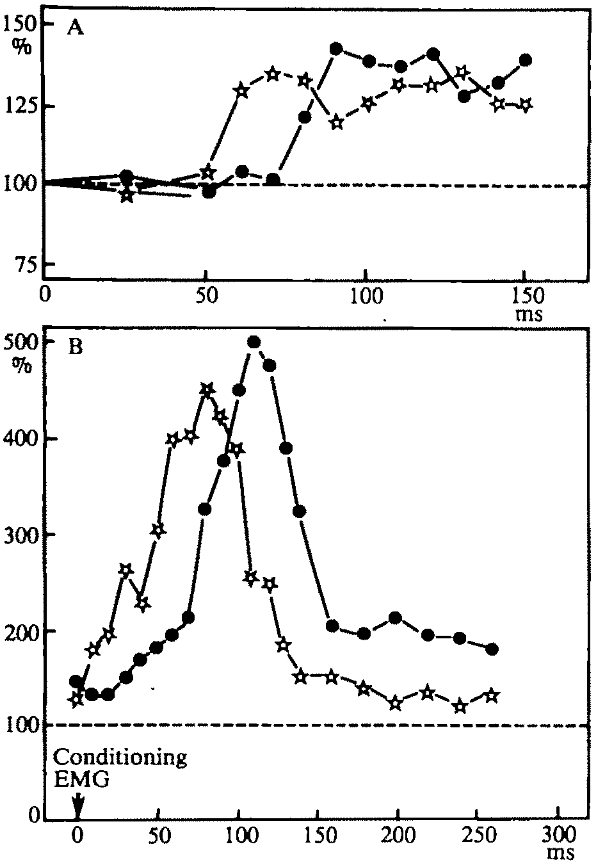

FIG. 7. Sequence of facilitation of monosynaptic reflexes in motor nuclei of masseter and quadriceps muscles (●). Results obtained in same subject during one experimental session. Conditioning by contraction of anterior compartment muscles of the lower leg contralateral to the test quadriceps reflex. A, phase I; B, phase II. Delays measured from start of conditioning contraction.

In plotting the curves, the peripheral conduction time of each reflex has been subtracted.

We have measured the latencies of onset of phase I (fig. 7A) and of the peak of phase II (fig. 7B). The curves of facilitation of masseteric and quadriceps reflexes following contraction of the dorsiflexors of the contralateral foot, obtained in the same experimental session, have been compared in 10 subjects.

(i) *Latency of onset of phase I.* Phase I appears earlier in the motor nucleus of the masseter than in that of quadriceps (fig. 7A). In individual experiments, facilitation in the quadriceps motor nucleus begins 10 to 20 s after that in masseter. As the distance separating the two nuclei is about 40 cm, the facilitation of phase I can be said to travel from above downwards at a velocity between 20 and 40 m. s^{-1}.

(ii) *Peak of phase II facilitation.* The onset of phase II is generally more difficult to define that the peak of facilitation and for this reason we have chosen to measure the latency of the latter. It has been shown above that the peak of phase II comes after the beginning of EMG activity in the conditioning muscle. Since there are variations in the delay between the command to contract and the appearance of EMG activity, it has seemed more accurate to time the peak of facilitation from the onset of contraction in the conditioning muscles (fig. 7B). The onset of EMG activity in the foot dorsiflexors has therefore been taken as time 0; the amplitudes of facilitation of the two motor nuclei were measured every 10 ms thereafter. Fig. 7B shows a characteristic example. Because of spontaneous fluctuations in the amplitude of the masseteric reflex, a large number of responses were recorded, each point in fig. 7B corresponding to the average of 20 measurements. Maximal facilitation of the masseteric motor nucleus precedes that of quadriceps. However, afferents coming from the conditioning muscles enter the spinal cord (L5) much nearer the quadriceps motor nucleus (L4) than that of the masseter. It therefore seems necessary to conclude that the afferent signals do not exert facilitation by means of segmental mechanisms, but rather that they descend from supraspinal centres to influence successively the masseteric and quadriceps motor nuclei.

The latency differences varied, according to the subject under study, between 25 and 50 ms. The distance of 40 cm between the two motor nuclei is therefore traversed by facilitatory activity at a velocity of 8 to 16 m. s^{-1}.

DISCUSSION

It has been shown previously that the degree of facilitation of a monosynaptic reflex by contraction of distant muscles is related to the time interval separating the command to contract and the elicitation of the reflex (Kawamura and Watanabe, 1975; Delwaide and Toulouse, 1980). The present results confirm this finding and indicate that the variations of amplitude with delay are fundamentally the same in soleus, quadriceps, and masseter when the conditioning contractions are identical (rapid onset, contraction maintained for 3 s). In these conditions, we have distinguished three phases (Delwaide and Toulouse, 1980). However, differences in intensity and latency of these phases can be observed according to the location of the conditioning contraction and test reflex.

The definition of three distinct phases depends, however, on the particular experimental conditions. For example, the difference between phases II and III is accentuated by more intense conditioning contractions. If the conditioning contraction is brief, only the first two phases can be distinguished. If, on the other hand, it increases slowly in strength, the amplitude of the testing monosynaptic reflex develops in a different way. If, finally, the conditioning voluntary contraction is prevented by blocking the motor nerve, a weak facilitation only occurs at phase I latency, and persists thereafter; while a conditioning tonic vibration reflex (motor conduction intact) evokes a moderate and stable remote facilitation. These findings suggest that it is possible to manipulate separately each phase of facilitation and thus to seek a particular mechanism for each. Separable mechanisms are also suggested by the differences between facilitation of the H-reflex and the soleus tendon reflex, which are parallel during phase II but clearly separate during phases III (Delwaide and Toulouse, 1980) and I (unpublished results).

Separable Facilitation Mechanisms in Each Phase

(a) *Phase I.* Phase I begins before the appearance of EMG activity in the conditioning muscles, and appears earlier in the motor nucleus of the masseter than in that of quadriceps. It corresponds to a slight increase in the amplitude of the testing monosynaptic reflex. It is seen in isolation when a voluntary command is directed to the conditioning muscles, even when these fail to contract because of conduction failure in motor fibres (radial paralysis or anæsthesia). On the other hand, phase I facilitation is not elicited by passive lengthening or vibratory stimulation of the wrist extensors. The intensity of facilitation observed in phase I depends on the tension developed by the conditioning contraction.

This phase of facilitation seems to be related to voluntary command. It may be part of a general phenomenon of motor facilitation. This facilitatory influence is likely to come from supraspinal structures but it is not possible to decide from our results whether it is of cortical or sub-cortical origin; it is transmitted by relatively slowly-conducting pathways.

(b) *Phase II.* Phase II, characterized by a peak of facilitation, is only clearly seen in cases where the conditioning contractions begin abruptly and are ballistic, or begin ballistically and are subsequently maintained. It starts always after the start of the conditioning contraction, and attains its maximum a 100 or so ms after the onset of the EMG in the conditioning muscles. It persists after the cessation of electromyographic activity, as in the case of ballistic conditioning. The more intense the conditioning contraction, the clearer the facilitation.

A marked facilitation, without preceding phase I, but assimilable to phase II, also appears 80 to 90 ms after rapid passive movements of the wrist.

Contrarily, phase II is not seen when the muscular contraction does not appear, despite maximum voluntary effort, because of radial paralysis. In this case, fig. 5 suggests that phase I facilitation is prolonged into the time normally occupied by phase II. Finally, blocking of the motor nerve to the conditioning muscles by injection of local anaesthetic powerfully depresses phase II facilitation.

Taken together, these results strongly suggest that the facilitation of phase II is related to proprioceptive afferent impulses set off by the muscle contraction, transmitted by group Ia and perhaps group II afferent fibres from muscle spindles. Discharges in these fibres constitute the common denominator of experimental situations which give rise to a peak of facilitation. In fact, voluntary contraction activates them very effectively (Vallbo, 1973; Hagbarth *et al.*, 1975; Burke, Hagbarth and Skuse, 1978; Vallbo, Hagbarth, Torebjork and Wallin, 1979), but other afferents (tendon organs, group Ib) are also activated, especially in conditions of isotonic contraction. But passive lengthening stimulates muscle spindles but not Golgi tendon organs (Vallbo *et al.*, 1979); it also activates joint afferents which on the other hand are not influenced by voluntary isometric contraction. The role of muscle afferents is also emphasized by the experiment involving blocking of the radial nerve by xylocaine. This was in fact incomplete and may be considered as affecting particularly the fusimotor fibres (Matthews and Rushworth, 1957). Activity in these fibres is necessary to bring about a large-scale discharge in groups Ia and II during voluntary contraction (Hagbarth *et al.*, 1975; Burke, Hagbarth, Löfstedt and Wallin, 1976). The absence of phase II in subjects suffering from radial paralysis can be interpreted in the same way because proprioceptive discharges of muscular origin cannot occur in this situation. The facilitation elicited by vibratory stimulation can also be understood in this light, since the effect can be attributed to proprioceptive afferents coming from muscle spindles. Thus the peak of facilitation in phase II can plausibly be attributed to discharge in group Ia (and perhaps II) fibres.

Furthermore, it is striking that all procedures which increase facilitation have also been shown microneurographically to augment the discharge of fibres of groups Ia and II. Thus when muscle tension increases, the discharge of Ia and II fibres increases in virtually linear fashion (Vallbo, 1973; 1974). This is clearly related to the result illustrated in fig. 1C, which shows that greater tension in the conditioning muscle correlates with an increase in the facilitation of the test reflexes. In ballistic movement, the discharge rate of spindle receptors is very high at the beginning of contraction, while in the case of gradually-developing contraction, Ia discharges also build up smoothly. It is thus tempting to attribute the peak to the grouped high-frequency discharge in Ia (and perhaps II) fibres which has been found to occur in those experimental conditions where there is a clear peak of facilitation.

(c) *Phase III.* This is best seen in the case of isometric contraction maintained for more than 600 ms. It is characterized by a facilitation of an intensity intermediate between that of phases I and II, and particularly by an amplitude which remains fairly stable until the end of the conditioning contraction. The height of the plateau thus sustained after the peak of phase II is more or less linearly related to the muscle tension of the conditioning contraction. On the other hand, phase III is lacking after a purely ballistic contraction as well as in subjects with paralysis or local anæsthesia of the radial nerve. A possible mechanism for phase III may be the activity of Ia afferents coming from the conditioning contraction as in phase II, but now in a tonic and lower frequency manner. Once again it is known from neurographic studies that the discharges are more regular and of lower frequency during maintained contraction, except at its inception (Vallbo, 1967; 1973). In fact, the dynamic component which is so effective in initiating discharge in Ia fibres is no longer evident after 600 ms. However, the identity of the mechanisms of phases II and III cannot be established until further research shows why the Hoffmann reflex is clearly facilitated during phase II but not during phase III. It is possible that other influences are at work during phase III. Thus the phase I facilitation of supraspinal origin may be prolonged until the end of voluntary contraction as suggested by observations in cases of radial nerve paralysis.

The Location of Facilitation-transmitting Circuits

Given that the remote facilitation of reflexes, maximal during phase II, is related to proprioceptive afferents coming from the conditioning muscle, one may speculate on the pathways followed by facilitatory Ia influences to produce their effect. Such pathways must be capable of transmitting information upwards or downwards, since similar effects are observed whether conditioning is performed by muscles in the upper or in the lower limb. Furthermore, it will be recalled that contraction on the side opposite the limb under test is as effective as ipsilateral contraction, which implies mechanisms acting at the same intensity bilaterally.

Propriospinal fibres are worthy of consideration in this light. Ventral and lateral fasciculi are known (Barilari and Kuypers, 1969: Rustioni, Kuypers and Holstege, 1971). In the cat, the *ventral fasciculus* originates in cells situated between segments C2 and C4 and terminates in segments L7–S1. Its cells are activated by vestibulospinal and reticulospinal pathways, as well as by tectospinal and interstitiospinal fibres. Armand and Kuypers (1980) have also described crossed corticospinal fibres ending on the same cells. The effects of this ventral fasciculus are chiefly exerted on the motoneurons of proximal muscles, bilaterally and equipotentially; it is responsible for the facilitation of both flexor and extensor motor nuclei (Vasilenko, 1975; Kostyuk and Vasilenko, 1979). The *lateral fasciculus*, studied by Jankowska, Lundberg, Roberts and Stuart (1974) and Illert *et al.* (1977, 1978) is excited by corticospinal and rubrospinal pathways; it acts mainly ipsilaterally on the motoneurons of distal muscles. The neurons of both these pathways are also activated by group Ia fibres (Kostyuk and Vasilenko, 1979), and are particularly sensitive to the mechanism of temporal summation. It can thus be easily imagined that they could transmit facilitation to lower limb motoneurons following activation by Ia afferent impulses coming from conditioning contraction of upper limb muscles. However, such an interpretation would not account for the caudo-rostral effects which have been observed since ascending propriospinal pathways have properties quite different from those of descending propriospinal pathways (Miller, Reitsma and Van der Meché, 1973). Furthermore, ascending pathways do not go above the C2 segment, and could not alone account for the phase II facilitation of the masseteric tendon reflex following contraction of the tibialis anterior.

Finally, Meinck, Roesler and Schomburg (1976) and Schomburg, Meinck and Haustein (1975) have shown that direct stimulation of the brachial plexus facilitates the motor nuclei of the lower limb and that these effects are transmitted by a descending propriospinal pathway. The same circuit cannot be involved in the transmission of facilitation following voluntary contraction, since in our experiments the effects are bilateral, and not, as in the experiments of Meinck *et al.* (1976), mainly ipsilateral to stimulation. Thus transmission in propriospinal pathways does not provide a satisfactory interpretation of all our experimental results.

It thus appears necessary to invoke supraspinal relays to explain the peak of facilitation in phase II. Only this could explain the sequence of facilitation observed in two separate motor nuclei following contraction of tibialis anterior: even when the primary afferents enter the cord close to the quadriceps motor nucleus, the peak of facilitation is seen first in masseter. In this case, latencies of 70 ms and more which separate the onset of EMG activity in the conditioning muscle and the peak of facilitation in phase II are compatible with a supraspinal circuit. It may be considered that the discharge of Ia fibres arrives 15 ms after the onset of contraction in the motor fibres (Vallbo *et al.*, 1979). A further 20 ms are necessary to reach the brain since Ia discharges follow rapidly-conducting pathways. The descending pathway on the other hand is more slowly-conducting. One is thus led to conceive that the maximal facilitation of a motor nucleus elicited by remote contraction is transmitted *via* a long loop made up of peripheral afferents, spinal ascending pathways, supraspinal relays, and descending spinal pathways.

Our results do not enable us to localize the level of the supraspinal relay, nor the descending pathways transmitting the facilitation. The study of selected pathological cases will eventually settle the question. At this stage, one may only speculate. The bilateral symmetry of the effects does not *a priori* imply a cortical relay. The descending facilitatory influences may be organized at bulbar level, in relation with cerebello-vestibular mechanisms. However, it is distinct from reticulo-vestibular impulses elicited by caloric stimulation of the labyrinths, for this type of facilitation, even though it may be bilateral, does not affect flexor muscles (Delwaide, 1977).

SUMMARY

The facilitation of the tendon reflex of quadriceps, induced by voluntary contraction of a muscle group in the upper limb, evolves in three phases and depends on several factors. These include the strength and type (ballistic or ramp) of the contraction. In the absence of any electromyographic activity in the conditioning muscle (from a lesion of its nerve trunk or by blockage of conduction by injection of xylocaine), a voluntary attempt to contract it causes only a moderate facilitation of the quadriceps motor nucleus; while reflex activation of the conditioning muscles, by vibration or sudden stretching, causes a more marked facilitation. Thus, it is concluded that at least two distinct mechanisms act sequentially. First, a general motor facilitation of supraspinal origin induces the first moderate phase of facilitation (phase I). This early facilitation precedes the onset of electromyographic activity in the conditioning muscle. Secondly, the more marked facilitation (phase II) is related to the stimulation of afferents originating from the conditioning muscles, either by fusimotor excitation in voluntary contraction or by manœuvres which stimulate the spindle receptors mechanically.

To investigate the transmission pathways of these facilitations, the latencies of these two phases were compared at two distant motor nuclei, the trigeminal motor nucleus and the quadriceps nucleus, following voluntary contractions of the tibialis anterior. Since the facilitations of the trigeminal motor nucleus precede those of the quadriceps motor nucleus, a slowly-travelling rostro-caudal facilitation is postulated during phase II when the facilitation is related to afferents coming from the contracting muscle. A long loop, therefore, is postulated to interpret the second phase of the facilitation curves.

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(*Received March 10, 1981*)

Brain (1981), **104**, 721–734

INTELLIGENCE AND LEFT HEMISPHERE DISEASE

THE ROLE OF APHASIA, APRAXIA AND SIZE OF LESION

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INTRODUCTION

PSYCHOLOGISTS have yet to agree on a definition of 'intelligence'. As Piercy (1969) states, 'many of the people most intimately concerned with the problem are strangely embarrassed by the request for a definition and prefer to offer a treatise instead'. However we define 'intelligence', it remains an abstract concept and cannot be known directly but only through 'intelligent' behaviour. Moreover, it is difficult to disentangle the elements of behaviour that are due to intelligence *per se*, and those that depend on the tools (linguistic, praxic, sensory) by which intelligence manifests itself. In a verbal task for example, it is almost impossible to establish where language ends and cognitive processes begin. In studying intelligence it is therefore important to ascertain the degree to which a test response may depend on these other aspects, in particular to language (which may theoretically be considered subordinate to general intelligence). Many experimental studies with brain-damaged patients have sought to relate intelligent performances to aphasia or apraxia. Other studies with aphasic or apraxic subjects, although not directly concerned with this problem, have contributed to our understanding of it, and yet no definite conclusions have emerged from this work.

Weisenburg and McBride (1935) reported that aphasic subjects performed poorly compared with other groups on verbal tests, but their performance varied widely on non-verbal tests, sometimes achieving near-normal scores. Arrigoni and De Renzi (1964) found that patients with constructive apraxia due to left hemisphere lesions (LH) had lower scores on Raven's coloured Progressive Matrices 47 (PM47) than any other group. Zangwill (1964) reported normal PM47 results for individual aphasics who were selected to represent every aspect of the aphasic syndrome, whilst Basso, De Renzi, Faglioni, Scotti and Spinnler (1973) found low PM47 scores in aphasics, but there was no correlation with severity of aphasia.

Alajouanine and Lhermitte (1964) studied 218 aphasic patients with the Wechsler Bellevue Performance Scale (WBPS): of those with IQ scores under 80, the majority (80 per cent) had constructive apraxia, which was present in only 15 per cent of the total sample. Orgass, Hartje, Kerschensteiner and Poeck (1972) reported that left hemisphere patients without aphasia did better on the WBPS than right hemisphere patients who, in turn, did better than left hemisphere patients with aphasia. De Renzi, Faglioni, Savoiardo and Vignolo (1966) found that aphasic patients generally performed poorly on the Weigl Test, their scores varying with the severity of their comprehension deficit.

The WBPS and the PM47 are the most widely used tests of intelligence in brain-damaged patients and available evidence indicates that aphasic or constructive apraxic subjects perform poorly on both these tests compared with other patient groups.

This study is concerned with the relationships between intelligence, aphasia and apraxia. These disorders are frequently associated with lesions of the left hemisphere, and therefore subjects were selected from a continuous series of patients with focal left hemisphere damage. We used two intelligence tests based on widely different concepts of intelligence: the WBPS, a performance test, and the PM47, a perceptual test. The Wechsler-Bellevue is a heterogeneous battery of 11 subtests which are not designed to measure different primary abilities although they are related to educational background. Conversely, PM47 is a homogeneous test designed to cover all the processes of reasoning without reference to educational standards.

Purpose

We proposed to answer the following questions: (i) to what extent do language or praxic performances influence left hemisphere patients' scores in the WBPS non-verbal subtests and on the PM47? (ii) what is the influence of the size and site of the left hemisphere lesion on a patient's performance on these tests?

MATERIALS AND METHODS

Subjects

The cases were drawn from a continuous series of 304 left hemisphere patients examined in our Aphasia Unit during the period from January 1977 to June 1978. We excluded 131 left hemisphere patients for the reasons set out in Table 1.

Of the 173 left hemisphere patients included in the experimental group 159 had had their first hæmorrhagic or ischæmic stroke, 8 had traumatic lesions and 6 had neoplastic disease. All were adults (mean age 54.9 years) with at least primary schooling (mean 7.4 years). Aphasia was evaluated and three aspects were considered.

(1) *Presence or absence of aphasia* was assessed by means of the Token Test (De Renzi and Faglioni, 1978). Normal limits of performance on this test were established using data from 215 control subjects, matched for age and education. Patients with scores falling below the 5 per cent performance level of this normal population were considered to be aphasic. According to this criterion 141 patients were classified as aphasic and 32 patients as non-aphasic.

Table 1. 131 Left Hemisphere Patients Excluded from the Experimental Group

10 patients with neoplasm incompletely removed surgically
15 ambidextrous or left-handers
21 unwilling to be tested
18 bad quality of CT scan
53 bilateral lesions
3 epileptics
2 illiterate
1 crossed aphasia
8 unclassifiable aphasic syndromes

(2) *Type of aphasia*, as reflected in the quality of speech outflow along the fluency/non-fluency dimension, was evaluated according to a clinical criterion based on some of the factors outlined by Goodglass and Kaplan (1972) such as rate of speech, length of phrase and articulatory difficulties. Patients were submitted to a Standard Language Battery currently used in our Aphasia Unit which assesses verbal expression, auditory verbal comprehension, and uses both reading and writing versions of tests which require the use or understanding of isolated words and sentences. Based on these test scores 60 left hemisphere patients were classified as non-fluent and 81 as fluent.

(3) *Overall severity of aphasia* was scored according to a compound scale covering oral expression and auditory verbal comprehension. This scale, ranging from 0 to 8, was weighted in favour of tasks requiring the use, or understanding, of sentences as opposed to isolated words. Patients scoring 0 to 3 were rated severe (S) aphasics (N = 55) and those scoring 4 to 8 moderate (M) aphasics (N = 86) (Basso, Capitani and Vignolo, 1979). The frequencies of the experimental groups are shown in Table 2.

All patients were tested for ideomotor apraxia with scores ranging from 0 to 20 (cutting score of 17 established on 40 normals, De Renzi, Pieczuro and Vignolo, 1966) and for constructive apraxia, with scores ranging from 0 to 20 (cutting score of 15 on 50 normals according to De Renzi and Faglioni, 1967). Table 2 classifies the left hemisphere patients according to presence/absence of aphasia, ideomotor apraxia and constructive apraxia.

Table 2. Group Frequencies and Prevalence of Apraxic Patients

	Total (*N = 173*)	*No apraxia* (*a*)	*Constructive apraxia* (*b*)	*Ideomotor apraxia* (*c*)	*Constructive and ideomotor apraxia* (*d*)
NA	32	27 (84%)	2 (6%)	3 (9%)	0
SF	31	10 (32%)	16 (52%)	17 (55%)	12 (39%)
MF	50	30 (60%)	15 (30%)	11 (22%)	6 (12%)
SNF	24	3 (13%)	17 (71%)	19 (79%)	15 (63%)
MNF	36	18 (50%)	15 (42%)	10 (28%)	7 (19%)

NA = non-aphasics. SF = severe fluent aphasics. MF = moderate fluent aphasics. SNF = severe non-fluent aphasics. MNF = moderate non-fluent aphasics. The group frequencies may be obtained subtracting (*d*) from the sum of (*a*), (*b*) and (*c*).

Testing Procedures

All the 173 patients included in this study underwent the following tests: (1) WBPS, i.e. picture completion (PC) (scores ranging from 0 to 15), picture arrangement (PA) (0 to 18), block design (BD) (0 to 18) and object assembly (OA) (0 to 17); (2) PM47 with a time limit of ten minutes (Basso *et al.*, 1973) with scores ranging from 0 to 36.

CT Scan Investigation

Within ten days of testing, all patients underwent a CT scan (EMI Scanner 1000) for two purposes: (1) to calculate the volume of the lesion, which was done by counting the EMI pixels (the dimension of which are 1.25 × 1.25 × 13 mm) per slide of the pathological area and adding these numbers to get the lesion volume. Possible sources of error in this procedure are related to the partial volume phenomenon (New and Scott, 1975) and to difficulties in precisely delimiting the pathological area. Patients with bilateral ventricular enlargement possibly due to a bilateral lesion were excluded from the study (*see* Table 1). When only the left ventricle was enlarged (this usually happened when the lesion was so near the ventricle that it actually joined it), we subtracted the volume of the right ventricle and added the difference to the left hemisphere lesion in order to have a more precise evaluation of the volume of the lesion; (2) lateral maps of the lesions were obtained from CT pictures following the method of Luzzatti, Scotti and Gattoni (1979). A lesion was defined as 'small' if the volume did not exceed 1100 (approximately 22.3 cc) and the antero-posterior diameter of the map reconstructed on the lateral surface of the hemisphere did not exceed 30 per cent of the total diameter. On the basis of these criteria we isolated 64 maps: 23 pertaining to non-aphasic subjects and 41 to aphasics.

Statistical Procedures

The data were subjected to a multivariate analysis of covariance (Anderson, 1958). For the main analysis we adopted a factorial design including presence/absence of aphasia, and for aphasics only, considered severity, type (fluent *versus* non-fluent), and interactions between these latter two factors. Dependent variables were WBPS and PM47 scores. In all the analyses we made corrections for age, education and length of illness. Ideomotor apraxia, constructive apraxia scores and the calculation of lesion volume were added to the concomitant variables in a further analysis. The bivariate hypotheses were checked by means of Wilks' criterion, approximated to the F-distribution according to Rao (1951); the difference between WBPS and PM47 scores was subjected to univariate analysis of covariance.

To check the influence of apraxia upon the interrelations between the intelligence tests and subtests employed we carried out a covariance analysis with a factorial design, including presence/absence of ideomotor apraxia, presence/absence of constructive apraxia and their interaction. The variables were the subtests of WBPS and PM47 scores and their relationship was studied by means of a profile analysis (Morrison, 1967). To exclude the influence of presence/absence of aphasia, only aphasic subjects ($N = 141$) entered this analysis. In addition we calculated the correlation coefficient between all the pairs of variables within the set of the psychological measurements plus the volume of the lesion. Because of the large number of coefficients, the significance level was set at 0.001 in order to keep the overall risk of type 1 error at the 0.05 level, following the Bonferroni inequality (Morrison, 1967). In addition, we calculated the partial correlation coefficients (Anderson, 1958) conditional on the Token Test values. This procedure allows the evaluation of the correlation between two variables after the removal of the common dependence from a third variable (in this case the Token Test scores).

The corrected PM47 scores of the 173 patients were ranked and the value corresponding to the 25th percentile was found (11.9). Of the 43 patients scoring less than the 25th percentile, 9 had 'small' lesions.

TABLE 3. MEANS OF THE CONCOMITANT VARIABLES IN THE 5 EXPERIMENTAL GROUPS

	Age	*Years at school*	*Length of illness (days)*	*Ideomotor Apraxia scores*	*Constructive Apraxia scores*	*Lesion volume (pixels)*
NA	57.18	6.78	162.78	19.40	18.53	347.34
SF	60.12	7.35	103.90	13.41	11.32	2325.10
MF	55.58	7.80	162.24	17.92	16.48	882.02
SNF	52.54	6.66	162.91	10.87	10.12	3617.21
MNF	49.16	7.91	383.80	17.27	15.30	1991.61

For abbreviations, *see* Table 2. Pixel = 1.25 × 1.25 × 13 mm.

RESULTS

Table 3 shows the means of all the concomitant variables employed, namely, age, education, length of illness, ideomotor apraxia, constructive apraxia and volume of lesion.

The mean scores achieved on PM47, WBPS and subtests of WBPS are presented in figs. 1 and 2. The results of the analysis of PM47 and WBPS scores are shown in Table 4. Both tests proved to be significantly affected by the presence and severity of aphasia, but not by its type.

When the second set of correcting variables (that is, volume of lesion and apraxia scores) is considered, the outcome of the covariance analysis shows that the presence of aphasia retains its significant role but that of severity is non-significant (Table 5).

Analysis of the significance of the corrections provided by the concomitant variables (Table 6) indicated that age, education and constructive apraxia were highly significant, whereas length of illness, volume of lesion and ideomotor apraxia did not affect the intelligence scores significantly.

TABLE 4. ANALYSIS OF COVARIANCE OF PM47 AND WBPS STANDARDIZED SCORES, ADJUSTED FOR AGE, EDUCATION AND LENGTH OF ILLNESS

	PM47 and WBPS scores (bivariate analysis)			*PM47 versus WBPS scores (univariate analysis)*		
Source of variability	*df*	*F*	*P*	*df*	*F*	*P*
Presence of aphasia	2,164	38.948	< 0.0001	1,165	< 1	ns
Type of aphasia (fluent *versus* non-fluent)	2,164	< 1	ns	1,165	< 1	ns
Severity of aphasia	2,164	11.191	< 0.0001	1,165	< 1	ns
Type × severity	2,164	< 1	ns	1,165	< 1	ns

ns = not significant

TABLE 5. ANALYSIS OF COVARIANCE OF PM47 AND WBPS STANDARDIZED SCORES, ADJUSTED FOR IDEOMOTOR APRAXIA, CONSTRUCTIVE APRAXIA SCORES, LESION VOLUME, AGE, EDUCATION AND LENGTH OF ILLNESS

	PM47 and WBPS scores (bivariate)			*PM47 versus WBPS score (univariate)*		
Source of variability	*df*	*F*	*P*	*df*	*F*	*P*
Presence of aphasia	2,161	13.515	< 0.0001	1,162	1.047	ns
Type of aphasia (fluent *versus* non-fluent)	2,161	< 1	ns	1,162	< 1	ns
Severity of aphasia	2,161	< 1	ns	1,162	< 1	ns
Type × severity	2,161	1.125	ns	1,162	< 1	ns

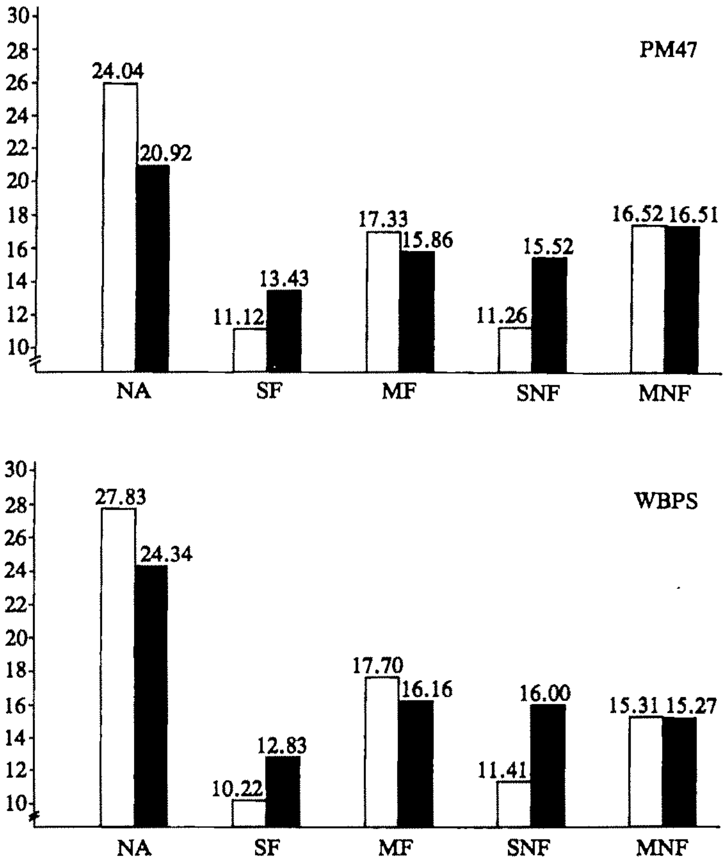


FIG. 1. Mean PM47 and WBPS scores achieved by the 5 experimental groups, adjusted for age, education and length of illness. Black column scores are corrected *even* for lesion volume, constructive apraxia and ideomotor apraxia. For abbreviations, *see* Table 2.

TABLE 6. ANALYSIS OF THE CORRECTIONS GIVEN BY THE CONCOMITANT VARIABLES

Source of variability	*df*	*F*	*P*
Correction of IMA	2,161	1.448	ns
Correction of CA	2,161	8.594	< 0.001
Correction of lesion volume	2,161	1.514	ns
Correction of age	2,164	15.190	< 0.0001
Correction of education	2,164	15.450	< 0.0001
Correction of length of illness	2,164	1.914	ns

IMA = ideomotor apraxia. CA = constructive apraxia.

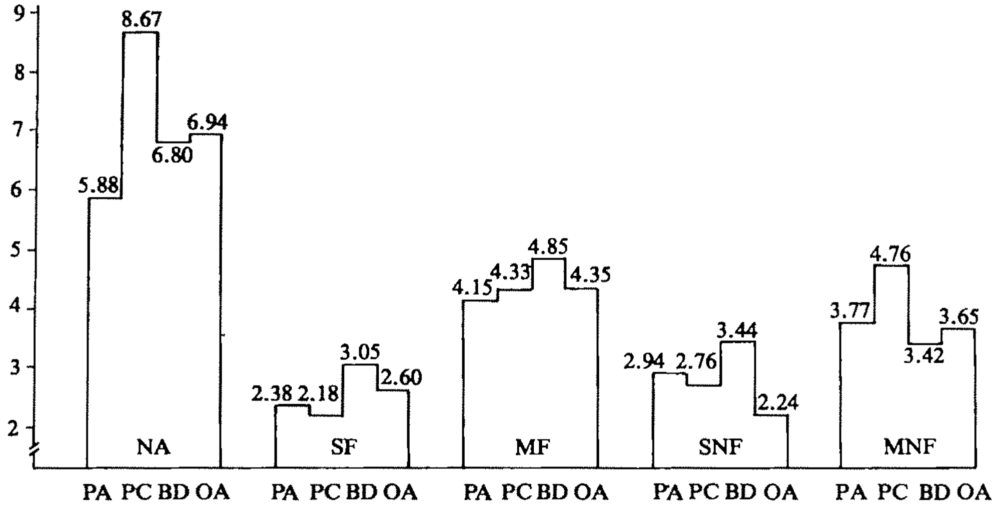


FIG. 2. Mean WBPS subtests scores achieved by the 5 experimental groups, adjusted for age, education and length of illness. For abbreviations *see* Table 7.

Table 7. Correlations Between the Psychological Scores and Lesion Volume Adjusted for Age, Education and Length of Illness (Upper Value). Lower Values Refer to Partial Correlations Obtained After Removing the Effect of Token Test Scores upon the Correlation of each Pair of Variables

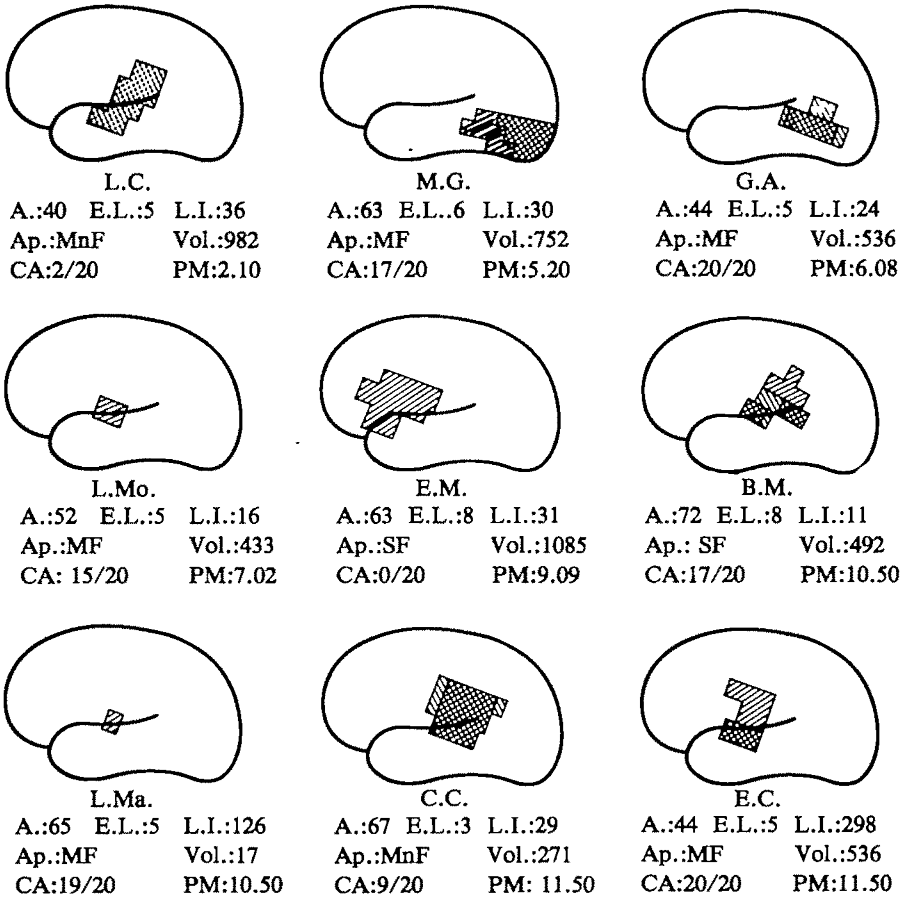
	PM47	*Wechsler PA*	*Wechsler PC*	*Wechsler BD*	*Wechsler OA*	*WBPS*	*Ideomotor apraxia*	*Construct. apraxia*	*Token Test*
Wechsler PA	0.59* 0.46*								
Wechsler PC	0.60* 0.41*	0.53* 0.38*							
Wechsler BD	0.57* 0.46*	0.47* 0.35*	0.43* 0.26*						
Wechsler OA	0.62* 0.52*	0.52* 0.42*	0.55* 0.42*	0.59* 0.51*					
WBPS	0.74* 0.62*	0.75* 0.67*	0.79* 0.68*	0.77* 0.72*	0.86* 0.84*				
Ideomotor apraxia	0.48* 0.30*	0.34* 0.17	0.46* 0.28*	0.39* 0.28*	0.38* 0.24*	0.49* 0.33*			
Constructive apraxia	0.54* 0.37*	0.50* 0.28*	0.50* 0.32*	0.47* 0.35*	0.40* 0.25*	0.56 0.40*	0.66* 0.53*		
Token Test	0.57* —	0.47* —	0.58* —	0.42* —	0.45* —	0.59* —	0.50* —	0.53* —	
Lesion volume	−0.43* −0.20	−0.32* −0.12	−0.33 −0.06	−0.30* −0.13	−0.29* −0.09	−0.38* −0.13	−0.57* −0.36*	−0.41* −0.13	−0.58* —

PA = picture arrangement. PC = picture completion. BD = block design. OA = object assembly.
* Significant (*see* Statistical Methods)

Inspection of the correlation coefficients (Table 7) shows very different values for the simple correlation coefficients and the partial correlation coefficients; the latter were obtained by removing the effect of the Token Test scores from the correlation between two variables. It appears that a considerable number of the correlations are explained by the underlying effect of aphasia and in the case of volume of lesion, that the effect of the latter is to a high degree mediated by the association between large lesions and low Token scores. This result is strengthened by the fact that when the volume is called to explain the data as first factor and aphasia as second, both have a significant role; this does not apply when the severity of aphasia is the first and the volume of lesion the second factor, since here only aphasia is significant. In the covariance analysis, the variance of the data, once the effect of volume of lesion was withdrawn, was again significantly reduced by the Token scores (F = 29.116, with 2,166 df, $P < 0.001$) whereas the opposite did not hold true (F = 2.236, with 2,166 df, non-significant).

The study of the influence of apraxia on the profile of the intelligence test scores showed that neither the presence of constructive apraxia (F = 1.388, with 4,130 df, P = non-significant), nor that of ideomotor apraxia (F = 1.039, with 4,130 df, P = non-significant) significantly affected the interrelation of these tests.

In order to study the relationship between site of lesion and intelligence test scores and to identify any crucial area related to poor performance, we selected from the 64 'small' lesions (*see* Methods) those left hemisphere patients with PM47 scores below the 25th percentile (9 subjects). As shown in fig. 3, only the frontal pole is not represented, simply because there were no patients with lesions in this region.



L.C.
A.:40 E.L.:5 L.I.:36
Ap.:MnF Vol.:982
CA:2/20 PM:2.10

M.G.
A.:63 E.L..6 L.I.:30
Ap.:MF Vol.:752
CA:17/20 PM:5.20

G.A.
A.:44 E.L.:5 L.I.:24
Ap.:MF Vol.:536
CA:20/20 PM:6.08

L.Mo.
A.:52 E.L.:5 L.I.:16
Ap.:MF Vol.:433
CA: 15/20 PM:7.02

E.M.
A.:63 E.L.:8 L.I.:31
Ap.:SF Vol.:1085
CA:0/20 PM:9.09

B.M.
A.:72 E.L.:8 L.I.:11
Ap.: SF Vol.:492
CA:17/20 PM:10.50

L.Ma.
A.:65 E.L.:5 L.I.:126
Ap.:MF Vol.:17
CA:19/20 PM:10.50

C.C.
A.:67 E.L.:3 L.I.:29
Ap.:MnF Vol.:271
CA:9/20 PM: 11.50

E.C.
A.:44 E.L.:5 L.I.:298
Ap.:MF Vol.:536
CA:20/20 PM:11.50

▨ Deep lesion ▧ Superficial lesion ▩ Deep + superficial lesion

FIG. 3. Lateral maps of the 'small' (*see* text) lesions belonging to the 9 left hemisphere patients whose PM47 scores were below the 25th percentile. Key: A = age. EL = educational level (years). LI = length of illness (days). Ap = aphasic syndrome. Vol = lesion volume (pixels). CA = constructive apraxia (score). PM = Raven PM47 score. MnF, MF, SF: *see* Table 2.

Finally, we looked for discrepant left hemisphere patients, that is, those with high constructive apraxia scores (higher than the cut-off score) and low PM47 scores (lower than the 25th percentile). We found 6 left hemisphere patients in each of these classifications (*see* Table 8).

Table 8. Subjects with High Constructive Apraxia Scores and Low PM47 Scores (under A) and Low Constructive Apraxia Scores and High PM47 Scores (under B). Constructive Apraxia and PM47 Scores are Adjusted for Age, Education and Length of Illness

No.	*Age*	*Sex*	*Education (yrs.)*	*Length of illness (yrs.)*	*Aph. Syn.*	*Token Test*	*Constructive apraxia*	*PM47*
(A)								
1	52	F	3	22	SF	10	18	4
2	57	M	5	41	SF	9	16	5
3	63	M	6	30	MF	29	18	5
4	62	M	5	126	MF	18	20	10
5	54	M	8	38	SNF	3	16	0
6	54	M	8	8	SF	7	18	6
(B)								
1	65	M	4	390	MF	11	8	22
2	15	F	9	49	MF	20	14	23
3	43	M	8	52	SNF	5	13	21
4	62	M	3	88	SNF	8	7	18
5	72	M	5	621	MNF	19	14	26
6	57	F	8	115	MNF	18	5	28

For abbreviations *see* Table 2.

DISCUSSION

1. *Relationship between Aphasia, Apraxia, and Intelligence Test Scores*

In line with previous data, the presence of aphasia has been shown to exert a significant influence on performance in the two intelligence tests employed, both of which gave similar results. Based on this evidence it appears that neither the type of aphasia, nor its severity, has a significant effect on intelligence test scores, once the scores were corrected for constructive apraxia. This result is difficult to explain and requires a definition of the role of constructive apraxia. We have the choice of two possible conclusions: (a) either that severely aphasic patients score less well than the moderately aphasic patients because the former group includes many constructively apraxic patients (*see* Table 2) who cannot perform well on the PM47 and WBPS because they have lost the ability to express cognitive processes which are still intact; alternatively, (b) that there are not different stages involved in performing the tests (that is, a cognitive processing and a praxic output). Constructive apraxic patients score poorly because constructive apraxia as a psychological construct is not distinguishable from intelligence (or because cerebral areas crucial for intelligence and eupraxia overlap). If the first hypothesis (a) were true, we would expect differences between the scores for the various intelligence tests to emerge since the relevance of constructive apraxia is reasonably assumed to be different for each test. Yet this is not so, for constructive apraxia correlates similarly with PM47 and WBPS and further, there is no significant difference between the constructive and non-constructive apraxic patients' profile across the tests. Finally, some subjects show a double dissociation between constructive apraxia and intelligence test scores (Table 8). Unfortunately, we cannot accept the second interpretation (b), because it depends heavily on the acceptance of the null-hypothesis, and we are forced to admit both that the experimental evidence does not clarify whether intelligence and constructive apraxia in left hemisphere patients are coincident constructs and, furthermore, that there is no support for the hypothesis of an overlapping localization of these functions (as will be detailed below). Thus, we have no choice but to leave these results uninterpreted.

2. *Relevance of the Site and Extent of Cerebral Lesion*

One of the most debated questions in clinical neuropsychology is the relationship between intellectual derangement and brain damage (*see* Lashley, 1929; Hebb, 1942), rendered more debatable by the lack of an acceptable definition of intelligence and by the paucity of techniques to reliably test aphasic left hemisphere patients. Accurate estimates of lesion volume, provided by CT scan information, were plotted against intelligence test scores and these results were statistically analysed. It is concluded that although larger lesions are more often associated with lower scores, the overall correlation (-0.20; -0.13, respectively, for PM47 and WBPS) is far too weak to support the concept of 'mass action' (Lashley, 1929), once the effect of aphasia has been withdrawn. Moreover, the demonstration that lesion volume acts largely through other variables leads us to a fundamental criticism of the validity of the concept of 'mass action' in humans, or, at least, casts doubts on its testability. Our results are not directly comparable to Tomlinson's (1977) correlation between pathology and intelligence test performance for methodological reasons, and also because his demented vascular patients had bilateral lesions. Patients with bilateral lesions, detected clinically or by CT scans, were excluded from the present study. The opposite approach, that is, the search for the site of small lesions in patients with low intelligence test scores (fig. 3) was equally unproductive, for the data point to no particular cerebral area that is either necessary or sufficient to ensure a low score. This study thus failed to bear out the conclusions of Basso *et al.*, (1973) (quoted by Lebrun and Hoops, 1974) that posterior areas of the left (as well as the right) hemisphere play a more important role in intelligent behaviour. Generally speaking, in the case of the left hemisphere it looks as if both the crude hypotheses of a definite 'centre' for intelligence and the alternative concept of the brain's equipotentiality are wide of the mark. Perhaps we should think in terms of a functional system which is able to carry out a task as long as a number of crucial cerebral areas are functioning; that none of these areas alone would be sufficient to carry out this function, but that many of them are to some extent equipotential and hence ready to take over in case of need.

In conclusion it seems that many factors contribute to disrupt what we have called intelligence. In clinical investigations such as ours, it is difficult to control for a number of these variables; for example, acquired pre-morbid training which might influence performance on abstract tasks, as well as other morbid factors that combine to reduce the redundancy of a set of competent areas below a critical point, either because the individual resources are already lowered, or, because the reallocation of a psychological process to a spared area can no longer take place. Moreover, it is possible that CT scan information may not reveal some lesions in cerebral areas that are actually not functional at the time of examination.

General Comment

The study of the relationship between intelligence and other variables (for example, aphasia and apraxia) can be viewed from two different perspectives and, accordingly, with different purposes. The analysis of the data can be aimed at finding the 'predictive value' of a given variable upon another variable, and this approach attempts to answer, for instance, the question of whether we should expect poor PM47 and WBPS scores among severe aphasics. Alternatively, the analysis may aim at finding 'causal' relationships, that is, at giving 'interpretations'; for example, one may wish to postulate that the intelligence deficits of left brain-damaged patients are 'linguistic' in nature.

The logic underlying these two conclusions is very different: a 'predictive' approach does not generally imply contradictions if two variables are associated with the same effect, whereas an 'interpretation' requires that one define sharply the role of each 'predictor' and often imposes choices between a number of possible explanations. In our case, we considered the roles of several variables on intelligence test scores in left brain-damaged patients. According to a 'predictive' perspective the results are clear-cut: presence and severity of aphasia and constructional apraxia are definitely associated with low PM47 and WBPS scores, but ideomotor apraxia and type of aphasia are not. In addition we did not find definite left hemisphere regions within which lesions were selectively associated with an intelligence deficit. With respect to the purpose of finding 'causes' for these defective performances, however, our data demonstrate that we cannot properly separate the roles of the largely overlapping factors, given above, in such a way that they can enter a definite heuristic model. Although we are able to give a relative value to the roles of aphasia and constructional apraxia as causative factors (or more simply as components) of an intelligence deficit, the indeterminacy of the real weight to be assigned to them is overwhelming. Generally speaking, the fact that these different possible causes are so intermingled makes it unlikely that the problem of the nature of the intelligence deficit of left hemisphere-damaged patients can be solved by this approach. The concept of an 'intelligence deficit' in left hemisphere-damaged patients as measured by PM47 and WBPS still remains ill-defined, and does not seem to be entirely coincident or comparable with the intelligence deficit of patients with 'diffuse' brain disease (for example, Alzheimer's disease), since even focal hemisphere-damaged patients with very low scores on these tests seldom behave as demented in everyday life. Nevertheless, the tests used in the present investigation are widely employed with focal brain-damaged patients, and thus we feel that although these results are apparently inconclusive for the purposes of theoretical progress, they may in fact provide useful information for a more critical and appropriate approach to the use of these psychometric tools.

SUMMARY

The Raven Progressive Matrices and four subtests of the Wechsler-Bellevue Performance Scale were given to 173 left hemisphere patients subdivided according to presence/absence, type (fluent/non-fluent) and severity (moderate/severe) of aphasia. Constructive and ideomotor apraxia scores and CT scan data of each subject entered the statistical analysis. Factors significant in producing a low score on Progressive Matrices and Wechsler-Bellevue were presence of aphasia and constructive apraxia. Site and size of lesion *per se* failed to account for the intelligence scores. The relationship between aphasia, apraxia, intelligence test scores, and CT scan data were discussed in an attempt to clarify the meaning of these low intelligence test scores in aphasics and to assess the underlying roles of the brain lesions in this deficit. It appears that there are a number of methodological difficulties complicating interpretation of the intellectual deficit based on the Progressive Matrices and Wechsler-Bellevue scores, since performance on these tests is adversely affected by both aphasia and apraxia.

ACKNOWLEDGEMENTS

We are grateful to Professor Arthur Benton for his helpful suggestions on a previous draft of this paper. Research was supported by a Grant from the Consiglio Nazionale delle Ricerche. Preliminary findings were presented at the Chianciano Meeting of International Neuropsychology Society (June 1980). Following our normal practice, names of authors are listed in alphabetical order, and this does not imply senior or junior authorship.

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(*Received October 2, 1980*)

Brain (1981), **104**, 735–752

WILSON'S DISEASE

AN ANALYSIS OF THE CRANIAL COMPUTERIZED TOMOGRAPHIC APPEARANCES FOUND IN 60 PATIENTS AND THE CHANGES IN RESPONSE TO TREATMENT WITH CHELATING AGENTS

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INTRODUCTION

WHEN Wilson (1911/12) published his original account of the disease which now bears his name the pathogenesis was unknown and any prospects of effective therapy must have seemed remote indeed. Wilson stressed particularly the lesions of the basal ganglia both from the clinical and the pathological points of view. The liver involvement he believed had little influence on the eventual outcome of the illness. Macroscopically he observed, in the brain, cystic changes in the putamen and globus pallidus. When cavitation was not found at post-mortem examination, the putamen, caudate and lenticular nuclei were commonly shrunken and often discoloured (Greenfield, 1957). Cortical changes have also been observed in the occipital lobes and in the frontal and prefrontal areas. Changes in the ventricles and brain-stem have not hitherto been recorded (*see* Cumings, 1959).

Proof by Cumings (1948) of the direct relationship between excess copper deposits in both brain and liver and the development of tissue damage in patients with Wilson's disease has led to a remarkable growth in our understanding of this disease and in the development of therapy which is effective in the great majority of cases (Walshe, 1956, 1976). It is now known that the first site of excess copper deposition is in the liver leading to the development of signs of hepatic disease in many cases (Chalmers, Iber and Uzman, 1957; Walshe, 1962) and that only later does the excess of this metal reach the brain leading to the wide spectrum of neurological signs and symptoms which are so characteristic of the illness. Studies with radioactive copper have delineated the natural history of this process (Walshe and Potter, 1977).

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On first attending the clinic about a third of all patients will complain of symptoms related to the liver and many of those presenting with neurological signs will give a history of an earlier attack of jaundice which resolved spontaneously, sometimes after many months. In these patients the main problem confronting the physician, once the diagnosis has been established, is that of prognosis. Whilst the great majority of patients can be saved by treatment with penicillamine the ultimate degree of functional recovery, it would be reasonable to assume, will depend upon the extent of the structural damage already suffered by the brain. It is widely held that there is no restoration of lost neurons so that it is clearly essential to start therapy before shrinkage, or worse still, cavitation has developed in the basal ganglia. Until recently there has been no way of determining this and it has not been possible, on clinical grounds, to judge the degree of restoration of function which can be expected in any given patient. The introduction of the EMI CT scanner offers the prospect of determining in advance which patients with neurological Wilson's disease can be expected to show a favourable response to treatment with chelating agents.

In this survey we report the cranial computerized tomographic (CT) appearances in sixty patients with Wilson's disease. Correlation of these appearances with the signs and symptoms at the time of scanning will be made and also the changes in response to treatment which were noted in the follow up scans. The role of CT in diagnosis and prognosis will also be discussed.

PATIENTS AND METHODS

Sixty patients with Wilson's disease were studied including all stages from presymptomatic through hepatic to those with an advanced neurological lesion. Their ages, at the time of first scanning, ranged from 9 to 67 years (mean 23 years). The examinations were performed initially using an EMI CT 1000 Scanner and subsequently an EMI 1010 Scanner. The basic principles of these systems have been described (Hounsfield, 1973; Hill, 1974). The patients have been subdivided into presymptomatic, 12 patients (these were diagnosed by genetic screening of affected families), hepatic, 8 patients and neurological, 40 patients. Nine of these patients had had no therapy at all at the time of first scanning and these included all three clinical types, 2 presymptomatic, 2 hepatic and 5 neurological. The remainder had all been on treatment with penicillamine (40 patients) or triethylene tetramine (11 patients).

The CT abnormalities were recorded under the following headings:

1. ventricular dilatation (having particular regard to the young age of the great majority of patients);
2. cortical atrophy and brain-stem atrophy, if dilatation of the cortical sulci or perimesencephalic cisterns were noted;
3. atrophy of the contents of the posterior fossa according to the criteria of Rothman and Glanz (1978), that is, accentuated cerebellar folia, fourth ventricular enlargement and widened posterior fossa cisterns;
4. particular attention was paid to the basal ganglia areas which are the site of maximal tissue damage (Wilson, 1911/1912; Greenfield, 1957).

RESULTS

1. *CT Appearances*

The CT findings for the various clinical subtypes of Wilson's disease are summarized in Tables 1, 2 and 3. The frequency of each particular abnormality is given in Table 4. The degree of abnormality has not been detailed but, not surprisingly, varied very considerably from one case to another and corresponded roughly to the severity of the illness at the time of diagnosis.

Ventricular dilatation (fig. 1A) was the most common abnormality being found in 73 per cent of cases. It was present in all categories and was frequently most marked in the frontal horns (fig. 1B). Invariably the dilation was present in the lateral ventricles, the third ventricle was also involved in severe cases. Cortical atrophy (fig. 2A), brain stem atrophy (fig. 2B) and cerebellar atrophy are all reflections of the

TABLE 1. SUMMARY OF CT FINDINGS IN 40 PATIENTS WITH NEUROLOGICAL WILSON'S DISEASE

Patient	*Sex*	*Age at onset (yrs)*	*Duration ℞ (mnths)*	*Severity of symptoms*	*Post. fossa atrophy*	*Brain-stem atrophy*	*Cortical atrophy*	*Vent. dilation*	*Basal ganglia lucency*	*Response to ℞*
E. An.	M	16	10	+	0	+	+	+	+	Incomplete
S. Bak.	M	11	120	**2+	0	+	+	+	+	Poor
G. Bal.	M	13	30	±	0	0	0	0	0	Good
A. Bar.	F	16	22	0	0	+	0	+	0	Good
J. Ba.	F	23	186	0	0	+	+	+	0	Good
S. Bi.	F	9	0	4^+	0	0	+	+	+	Good
A. Bo.	M	18	4	3^+	0	+	+	+	+	Poor
Pa. Br.	M	22	18	2^+	0	+	+	+	+	Incomplete
Ph. Br.	M	21	8	4^+	+	+	+	+	+	V. poor
A. Ca.	F	26	0	2^+	0	0	+	+	+	Good
J. Co.	F	21	0	3^+	0	0	0	+	+	Delayed
D. Cp.	M	17	156	0	+	+	+	+	+	Good
A. D.	F	16	3	4^+	0	0	+	+	+	Good
S. F.	F	24	0	+	0	0	0	0	+	Good
A. G.	M	9	156	0	0	0	+	0	0	Good
E. Gb.	F	20	27	0	+	+	+	+	0	Good
S. Ka.	M	19	157	0	0	+	+	+	0	Good
A. K.	M	13	189	0	0	0	+	+	0	Good
H. L.	F	12	198	0	0	0	0	+	0	Good
G. Ly.	M	12	11	2^+	0	+	0	+	0	Good
J. M.*	F	15	< 96	2^+	0	+	+	+	+	Incomplete
P. W. Mm.	M	13	34	+	0	+	+	+	+	Good
A. Mo.	M	40	65	0	0	+	+	+	+	Good
M. Na.	F	15	25	0	0	0	+	+	+	Good
K. Pe.	M	26	66	±	0	+	+	+	0	Good
A. Pk.	M	15	60	0	0	+	+	+	+	Good
M. Ro.	M	13	100	0	0	0	0	+	0	Good
D. S. (A).	F	13	83	±	0	0	0	+	+	Good
C. Sy.	F	25	53	0	+	+	0	+	+	Good
B. S.	M	21	78	0	0	+	+	0	0	Good
J. Sm	F	12	81	0	0	0	0	0	0	Good
C. So.	F	26	11	2^+	0	+	+	+	+	Slow
M. Sz.	M	10	194	2^+	0	+	0	+	0	Incomplete
J. Tu.	F	15	250	0	0	+	+	+	+	Good
M. Wk.	F	16	120	±	+	+	+	+	+	Good
J. Wb.*	F	16	< 48	+	0	0	+	+	0	Fair
C. Wh.	F	21	92	0	0	+	+	+	0	Good
J. Ws.	M	11	11	0	+	+	0	+	+	Good
S. Wy.	F	13	280	±	0	+	+	+	0	Good
S. Coh.	M	37	264	2^+	0	+	+	+	+	Incomplete

** Also sustained a skull fracture with residual hemiplegic symptoms. * Difficult to assess amount of ℞ : J.M. is a very poor complier: J.Wb. has had a number of toxic reactions.

widespread brain damage which can occur in this disease. It is probably because the brain damage is so widespread, particularly throughout the cortex, that many patients develop personality changes. Hypodense areas were seen in the basal ganglia in 45 per cent of cases (fig. 3A) but increased density due to copper deposition in this or other regions was not observed. The correlation of these basal ganglia hypodense areas with other CT abnormalities is to be found in Table 5 and it will be seen that such associations are the rule rather than the exception; in fact only once in 27 cases were basal ganglia hypodensities found as an isolated abnormality. Eighteen per cent of patients had a normal scan including two with neurological signs.

2. *Correlation of Clinical and CT Findings*

It can be seen from Table 6 that abnormal CT appearances in patients with Wilson's disease are commonest in patients with a neurological presentation but are also present in the hepatic and even the presymptomatic groups (fig. 3B). Half the presymptomatic and three-quarters of the hepatic patients showed more than one abnormality on CT scanning whereas only 2 out of 40 neurological patients were completely normal, and as both these had been on treatment with penicillamine for more than two years it is possible that basal ganglia hypodensity, which had been

TABLE 2. SUMMARY OF CT FINDINGS IN 8 PATIENTS WITH HEPATIC WILSON'S DISEASE

Patient	*Sex*	*Age at onset (yrs)*	*Duration ℞ (mnths)*	*Severity of symptoms*	*Post. fossa atrophy*	*Brain-stem atrophy*	*Cortical atrophy*	*Vent. dilation*	*Basal ganglia lucency*	*Response to ℞*
E. Bar.	F	14	22	0	0	0	+	+	+	Good
D. Ch.*	M	10	39	0	0	0	0	0	0	Good
J. Col.	F	15	0	3^+	0	+	+	+	0	Good
C. Cr.	F	9	187	0	0	0	+	0	0	Good
T. L.	F	10	23	0	0	0	0	0	0	Good
D. Sp.	F	8	127	0	0	0	+	+	0	Good
S. Tp.	M	12	165	0	0	+	+	+	0	Good
S. To.	M	18	0	2^+	0	+	+	0	0	Good

TABLE 3. SUMMARY OF CT FINDINGS IN 12 PATIENTS WITH PRESYMPTOMATIC WILSON'S DISEASE

Patient	*Sex*	*Age at onset (yrs)*	*Duration ℞ (mnths)*	*Severity of symptoms*	*Post. fossa atrophy*	*Brain-stem atrophy*	*Cortical atrophy*	*Vent. dilation*	*Basal ganglia lucency*	*Response to ℞*
K. Br.	M	16	0	0	0	+	+	+	0	
P. Ch.*	M	10	39	0	0	0	0	0	0	Well
A. Kar.	F	9	60	0	0	0	0	+	0	Well
S. LA.	M	23	0	0	0	0	0	0	0	Well
S. Ly.	M	11	0	0	0	0	0	0	0	Well
P. Ma.	M	19	93	0	0	+	+	+	+	Well
R. M.	M	11	190	0	0	+	+	+	+	Well
V. N.	F	15	120	0	0	0	0	0	0	Well
D. Pe.	M	25	66	0	0	0	0	0	0	Well
P. Sh.	M	12	36	0	0	0	0	0	0	Well
W. Sh.	M	11	36	0	0	0	0	0	0	Well
J. Tv.	M	18	94	0	0	0	+	+	+	Well

* Identical twins.

present initially, had resolved. The oldest patient in this series, aged 67 years, showed advanced lesions in the basal ganglia, cortex and ventricles. Clinically he had a moderately severe parkinsonian syndrome: he had had a prolonged illness before the correct diagnosis had been made and therapy started. However, it may well be that senile changes are superimposed on those due to his Wilson's disease, (fig. 4).

Table 4. Incidence of Cranial CT Abnormalities in 60 Patients with Wilson's Disease

Lesion	*No.*	*Percentage*
Ventricular dilation	44	73
Cortical atrophy	38	63
Brain-stem atrophy	33	55
Basal ganglia hypodensity	27	45
Posterior fossa atrophy	6	10
Normal	11	18
Basal ganglia hyperdensity	0	

Table 5. Association of Basal Ganglia Hypodensity with other CT Abnormalities in 60 Patients with Wilson's Disease

Lesion	*No.*
Hypod + VD/CA/BSA/PFA	3
Hypod + VD/CA/BSA	12
Hypod + VD/CA	7
Hypod + VD	2
Hypod + CA/PFA	1
Hypod + BSA/PFA	2
Hypod alone	1

Key

Hypod = Basal ganglia hypodensity
VD = Ventricular dilation
CA = Cortical atrophy
BSA = Brain-stem atrophy
PFA = Posterior fossa atrophy

Table 6. Correlation of CT Abnormalities with Clinical Presentation of 60 Patients with Wilson's Disease

Lesion	*Neurological (40)*		*Hepatic (8)*		*Presymptomatic (12)*	
	No.	%	*No.*	%	*No.*	%
Vantricular dilation	35	90	4	50	5	42
Cortical atrophy	28	70	6	75	4	33
Brain-stem atrophy	26	65	3	37.5	3	25
Basal ganglia atrophy	23	57	1	12.5	3	25
Posterior fossa atrophy	6	15	0		0	
No abnormality	2	5	2	25	7	59

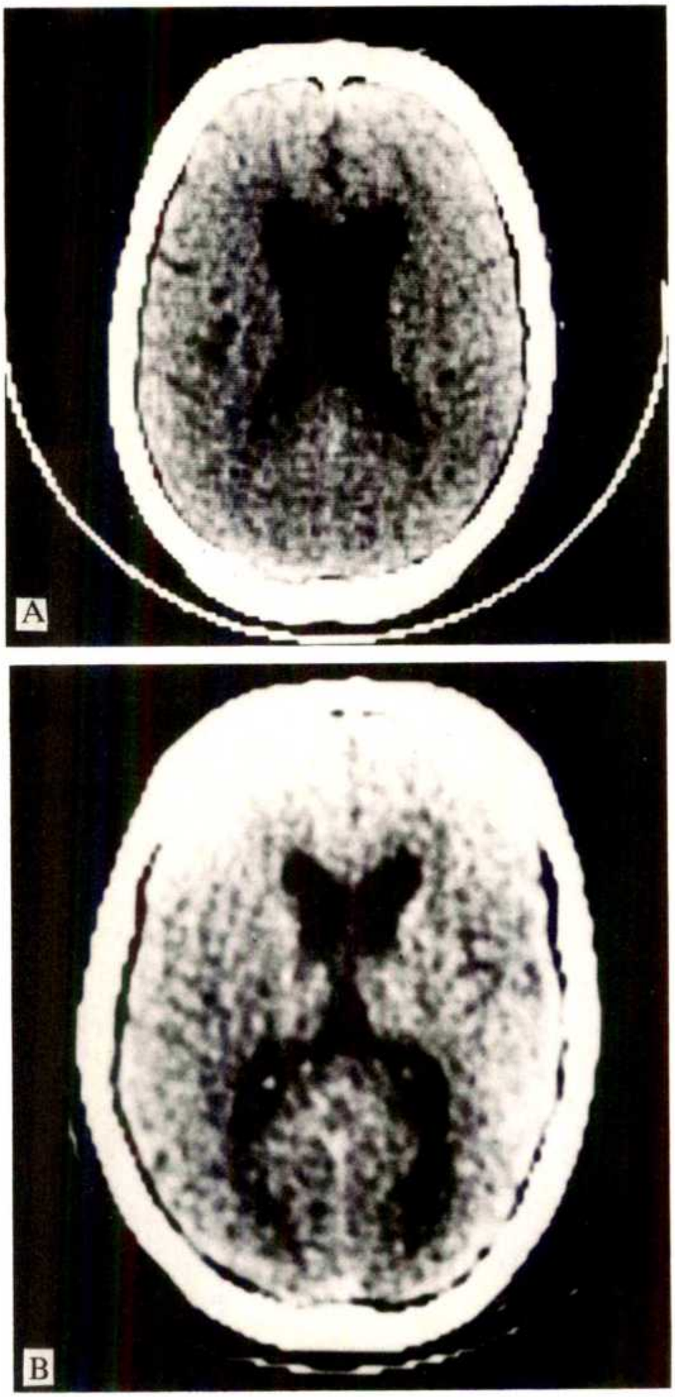


FIG. 1. A, ventricular dilation. Symmetrical dilation of the lateral ventricles in a 21-year-old male patient (Ph. Br., Table 1). B, anterior horn dilation. Focal bilateral dilation of the anterior horns with loss of normal concavity caused by the caudate nucleus. Female patient aged 18 years (A. Bar., Table 1).

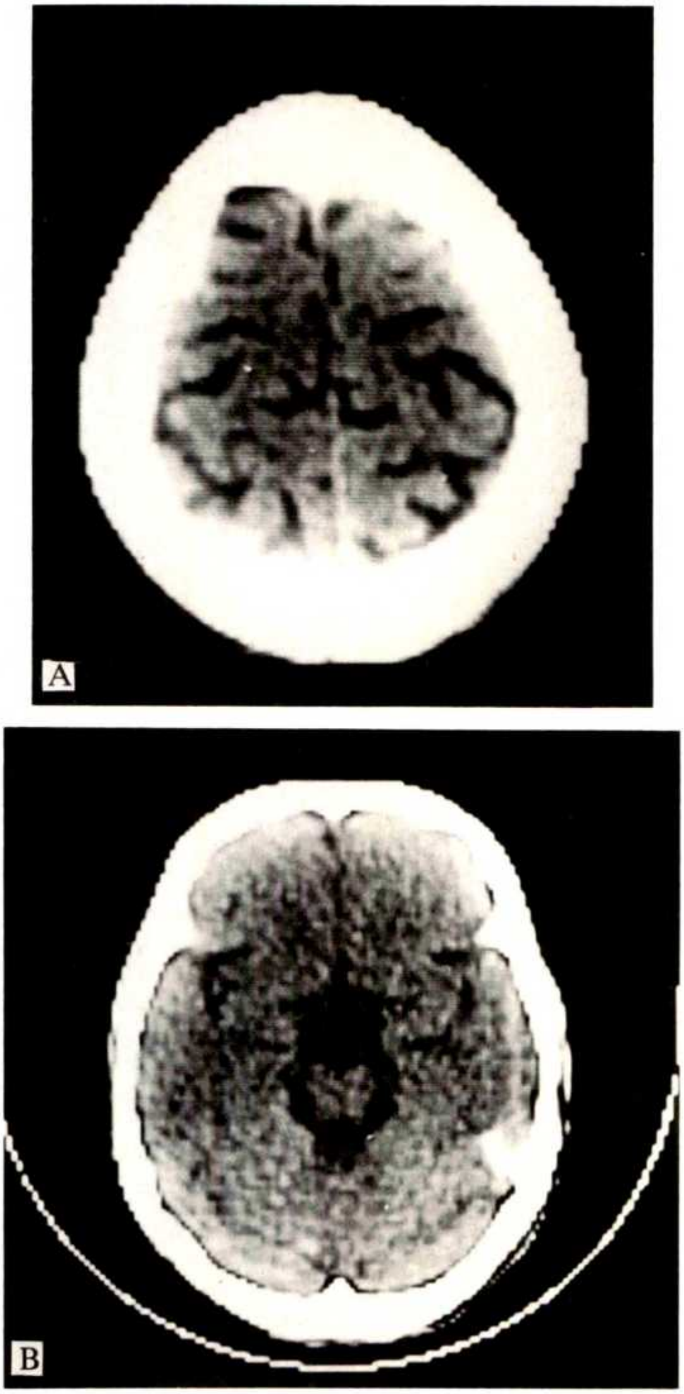


FIG. 2. A, cortical atrophy. Marked bilateral cortical atrophy in a 19-year-old male patient (P. W. Mn., Table 1). B, brain-stem atrophy. Symmetrical widening of the perimesencephalic cisterns. Female patient aged 26 years (C. So., Table 1).

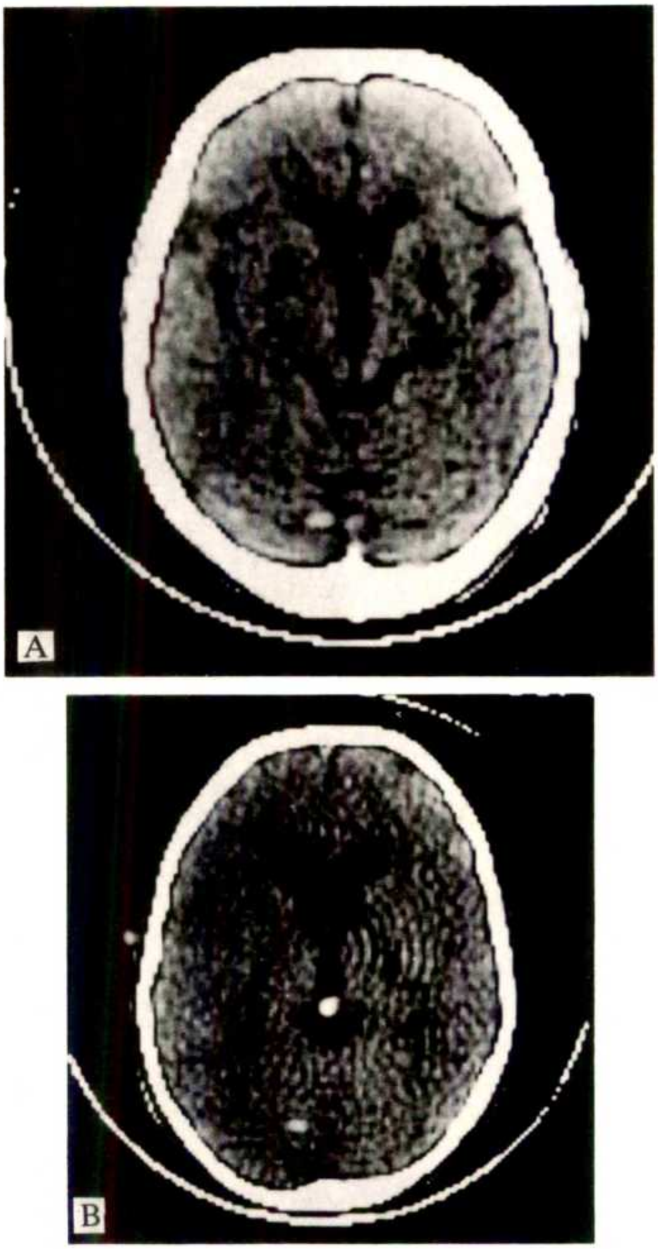


FIG. 3. A, basal ganglia hypodensities. The bilateral hypodensities and accompanied in this case by accentuated cerebellar folia, slight ventricular dilation and dilation of the basal cisterns and sylvian fissures (C. So., Table 1). B, abnormal CT in presymptomatic patient. Marked ventricular dilation female patient aged 14 years (A. Kar., Table 3).

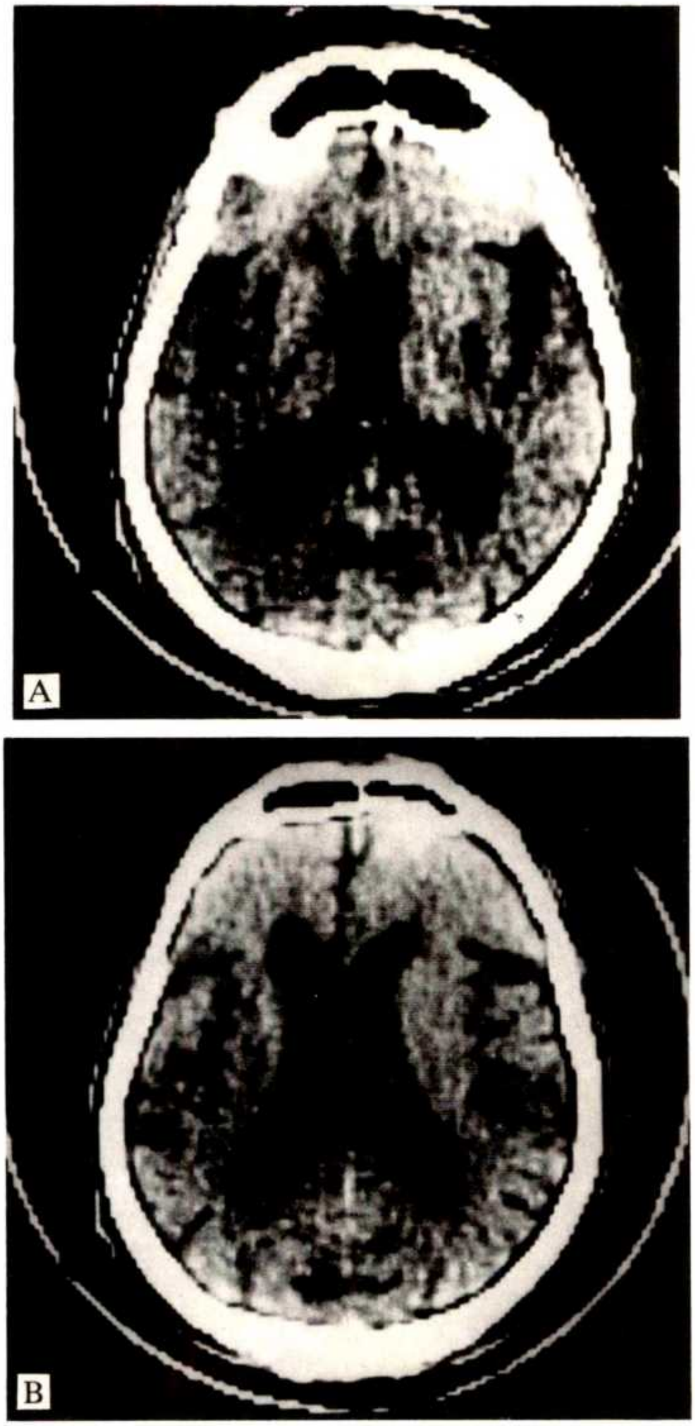


FIG. 4. 67-year-old male patient with A, bilateral basal ganglia hypodensities and dilated *iii* ventricle. B, dilation of the lateral ventricles and cortical sulci. In addition there is probably superimposed evidence of multi-infarct disease (S. Ch., Table 1).

3. *Response to Treatment*

Nineteen patients had follow-up scans (Table 7) to assess the effects of treatment with either penicillamine (14 cases) or triethylene tetramine (5 cases) on the abnormalities recorded initially. Fourteen of these patients showed hypodense areas in the basal ganglia and in 11 of these improved or became completely normal. This correlated well with the marked clinical improvement shown by all these patients (fig. 5). Indeed in one case the hypodense areas were so marked as to suggest cavitation (fig. 6A) and the clinical condition on admission appeared terminal with no co-ordinated movement, anarthria and severe dysphagia. One year later CT scan showed a remarkable improvement in the basal ganglia zones (fig. 6B) and the patient had made a complete clinical recovery (fig. 7). One patient, who was very slow in responding to treatment, showed some temporary worsening in the basal ganglia appearances before clinical and CT recovery set in. Of the other abnormal parameters recorded, virtually no changes were observed. One patient had a normal scan on two occasions a year apart.

TABLE 7. CHANGES IN CRANIAL CT SCANS IN 18 PATIENTS WITH WILSON'S DISEASE IN RESPONSE TO CHELATION THERAPY

	Basal ganglia hypodensity		
Patient	*1st scan*	*2nd scan*	*Therapy*
E. An.	+	0	Pen'amine
S. Bi.	+	±	Pen
Pa. Br.	+	+	TETA
Ph. Br.	+	+	Pen
A. Ca.	+	±	TETA
J. Co.	+	±	Pen
A. D.	+	±	Pen
S. F.	+	0	TETA
E. Gb.	0	0	TETA
S. L-A.	0	0	Pen
J. M.	+	+	Pen
P. W. Mn.	+	0	TETA
M. Na.	+	±	TETA
D. S. (A).	+	±	TETA
C. Sy.	+	0	Pen
C. So.	+	0	Pen
J. Wb.	0	0	Pen
C. Wh.	0	0	Pen
No. abnormal	14		
No. improved		11	
No. worse		1	

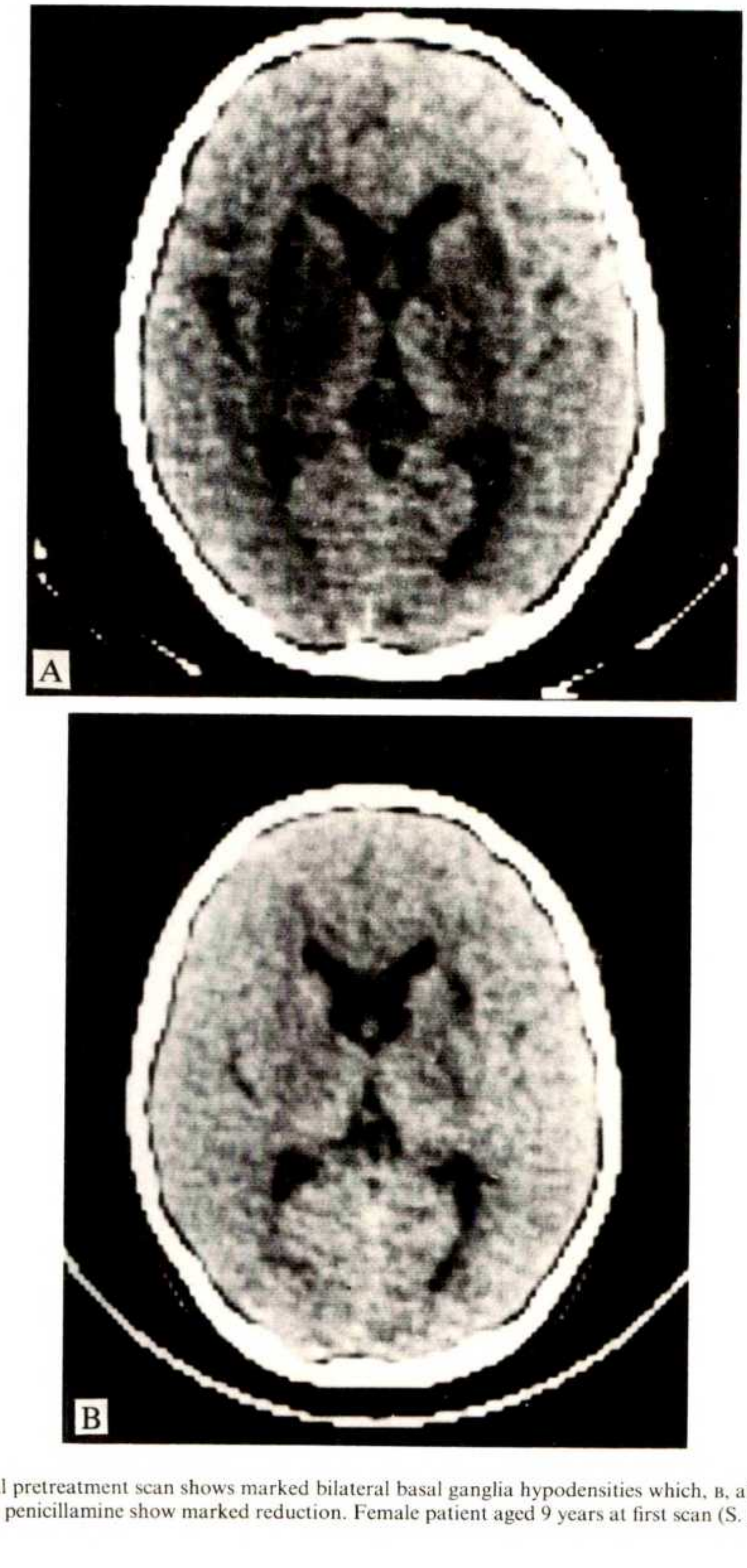


FIG. 5. A, initial pretreatment scan shows marked bilateral basal ganglia hypodensities which, B, after ten months therapy with penicillamine show marked reduction. Female patient aged 9 years at first scan (S. Bi., Table 1).

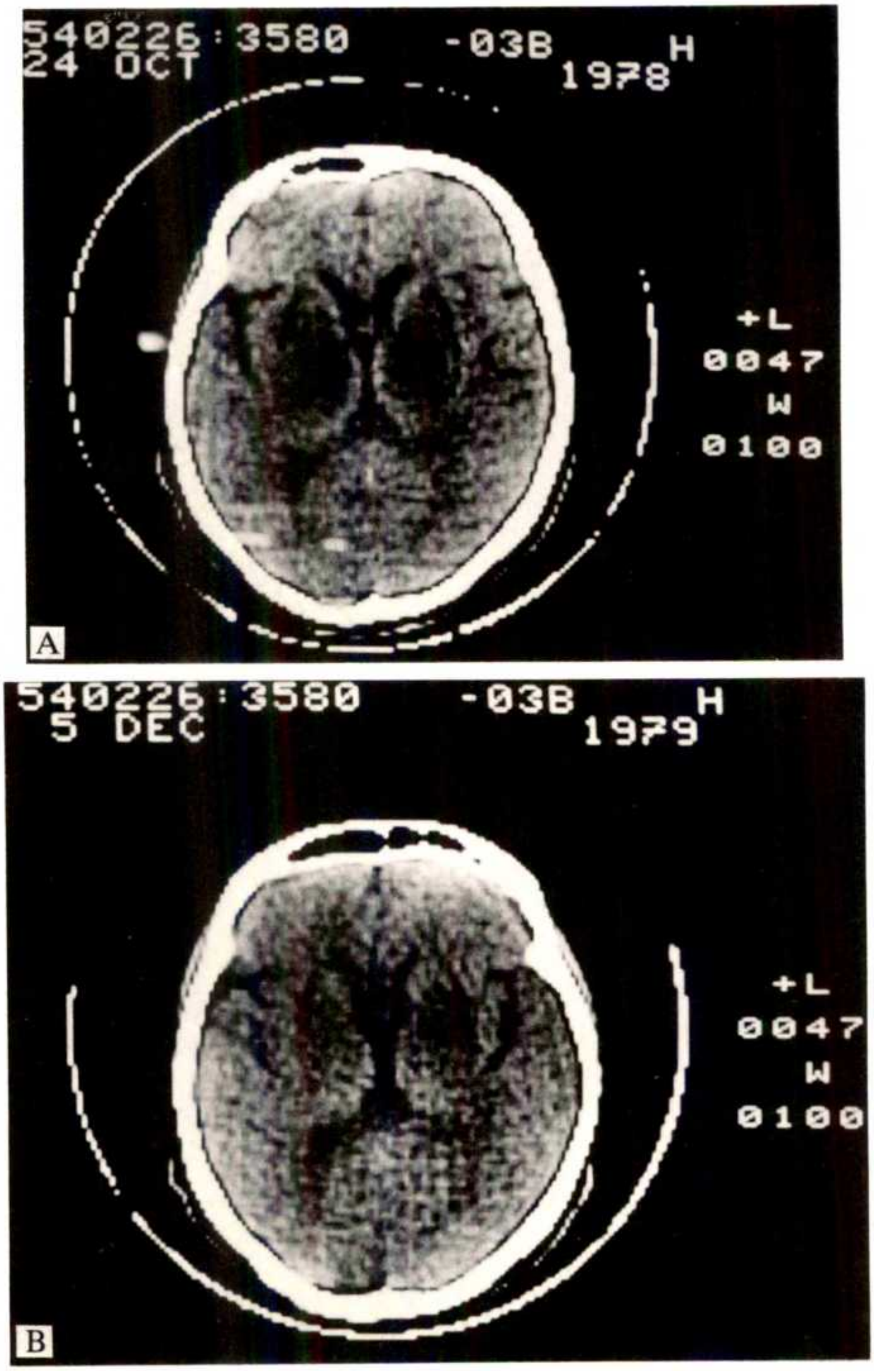
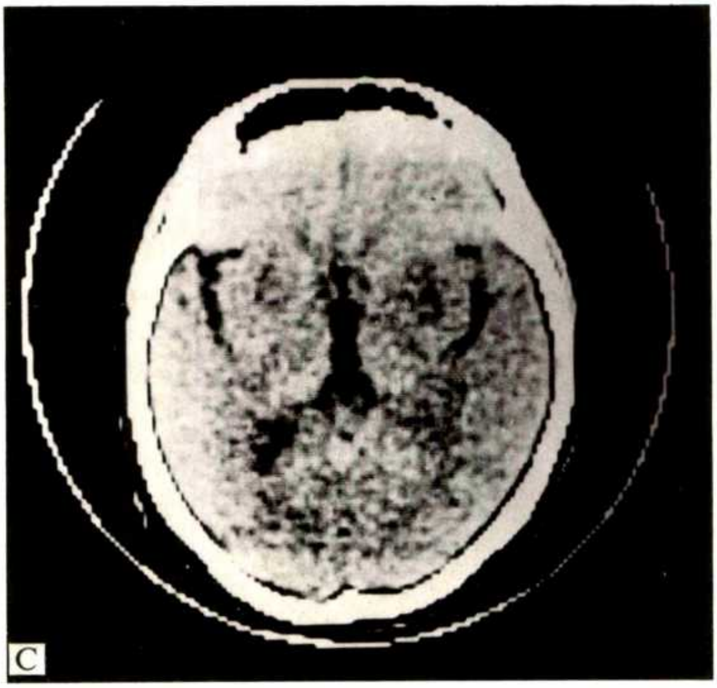
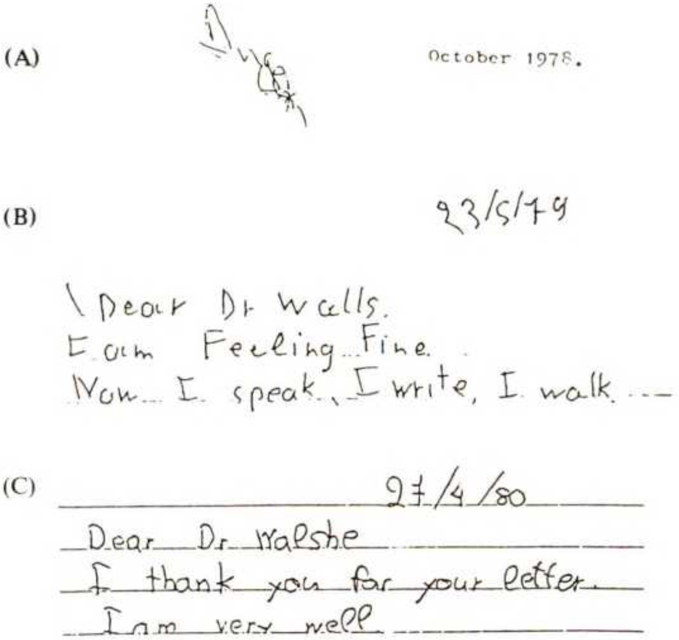


FIG. 6. A, B and C, scans before and seventeen and thirty-three months after starting treatment with penicillamine. Note that the hypodensities have shown a remarkable and continuing improvement but there has been no decrease in the size of the Sylvian fissures and the third ventricle may be a little larger. Female patient A. D., Tables 1 and 7. (*See also* fig. 7).





(A)

October 1978.

(B)

23/5/79

Dear Dr Walls.
I am Feeling Fine.
Now I speak, I write, I walk ...

(C)

27/4/80

Dear Dr Walshe
I thank you for your letter
I am very well

FIG. 7. A, handwriting of A. Da. before therapy. B, after seven months. C, after seventeen months, demonstrating the correlation between CT appearances and the clinical improvement of this patient.

DISCUSSION

To date there is no published description of CT changes in the brain in a large series of patients with Wilson's disease. Small series have been published by Kendall, Claveria and Quiroga (1977), 3 cases; Merland, Chiras, Melki and Cassan (1978) 9 cases, and Nelson, Guzman, Grahovac and House (1979) 7 cases. In Kendall's series two patients were normal and the third showed increased attenuation of up to 200 hounsfield units in the thalamus. Whilst increased copper deposition might be expected to produce such a hyperdense area resulting from increased attenuation neither the 16 cases comprising Merland's and Nelson's combined series nor the 60 cases in our own have revealed such an abnormality nor have we seen this in 35 additional cases studied since the present analysis was completed. On the other hand hypodense areas in the region of the basal ganglia appear to be common: Merland found 4 out of 9 and Nelson 3 out of 7 whilst we found this abnormality in 27 out of 60 or, if the presymptomatic cases are discounted, 24 out of 48, giving an overall total of close on 50 per cent. These changes presumably represent damage caused in the basal ganglia by the excess copper deposition. However, the other findings we have recorded, ventricular dilatation and generalized atrophic changes, indicate widespread brain damage. This should not cause surprise in view of the widespread deposition of copper throughout the grey matter of the brain (Warren, Earl and Thompson, 1960). It is probably significant that the ventricular dilatation was most prominent in the anterior horns, with loss of the concavity normally caused by the caudate nucleus (figs. 2 and 6).

This alteration of contour reflects further the tissue damage and atrophy in the caudate component of the basal ganglia. One patient only in this series has come to post-mortem and although the CT appearances of hypodensity of the basal ganglia were confirmed by the finding of necrosis and early cavitation the situation is complicated by the fact that he suffered a cardiac arrest three weeks before he died, an episode from which he never regained consciousness so that it is possible that the changes in the basal ganglia resulted from this rather than from his incompletely treated Wilson's disease.

The 4 remaining cases in Nelson's series were all suffering from hepatic Wilson's disease and all had normal scans. In Merland's series the 5 cases with normal basal ganglia all had cortical atrophy; all 5 cases had neurological symptoms. The findings from our own much larger series (Table 4) show clearly that all the abnormalities recorded in patients with neurological lesions may be found not only in the hepatic but also in the presymptomatic stage of the disease whilst, very occasionally, patients with neurological lesions may have a normal appearance to their CT scan.

The CT appearances we have recorded in patients with Wilson's disease may be seen in other conditions. The hypodense areas are the most specific and are almost invariably seen together with other CT abnormalities (Table 3). Only one patient in our series had low density areas in isolation. Leigh's disease (subacute necrotizing encephalomyelopathy) (Hall and Gardner Medwin, 1978) shows similar hypodense areas but this rare condition is commonest in infants whilst the biochemical lesion involving copper is absent. Infarction occurring bilaterally in the basal ganglia can give rise to similar appearances and may be seen after prolonged systemic hypotension (Matsuo, Cumings and Anderson, 1979), as a sequence of methanol intoxication (Aquilonius, Askmark, Enoksson, Lundberg and Moström, 1978) and also in sickle cell disease (Hall, K., personal communication). Basal ganglia cavitation has also been described in Parkinson's disease (Kendall *et al.*, 1977) but clinical confusion is unlikely. The typical findings in Huntington's chorea are of dilation of the frontal horns of the lateral ventricles resulting from caudate atrophy but hypodense areas in the region of the basal ganglia and brain-stem changes have not been reported (Terrence, Delaney and Alberts, 1977; Barr, Heinze, Dobben, Valvassori and Sugar, 1978). We believe that, in the appropriate clinical context, the hypodense areas together with generalized atrophy are characteristic of Wilson's disease.

In the absence of histological confirmation it is perhaps not entirely profitable to speculate on the nature of the pathological changes proceeding in the basal ganglia which leads to the development of the hypodense areas. The most likely explanation would seem to be loss of neurons leading eventually to cavitation; the appearances illustrated in figs. 5 and 6 would seem to support this. Both these patients, however, made quite spectacular clinical recoveries with a corresponding improvement in the CT appearances, in both cases in less than one year. It is difficult to believe that neuronal regeneration can have been responsible but it is equally difficult to find a convincing alternative explanation. Perhaps the most likely state of affairs is an extensive loss of dendrites, as has been reported in chronic alcoholism (Walker, Barnes, Riley, Hunter and Zornetzer, 1980), and of glial cells, and that these elements are initially replaced by exudate, later regenerating relatively rapidly when the excess of toxic copper is removed by chelation therapy. In patients who have residual low density areas after several years of therapy which has been associated with biochemical and often clinical improvement, it seems likely that the changes represent loss of neurons.

Whilst this series shows that CT brain scanning is of considerable value as a diagnostic tool in Wilson's disease, particularly in the problem areas of presymptomatic and hepatic cases, it is of little help prognostically. This is particularly so in view of the marked degree of recovery which can occur in the basal ganglia and the fact that extensive cortical atrophy can be present in patients apparently without intellectual damage. Even those who have never had signs or symptoms relative to the central nervous system may show CT changes. It is not safe to assume that a patient will not respond to therapy because of extensive atrophic changes in the CT scan; equally some patients have been seen whose CT scan showed only minimal abnormalities but whose clinical course has been disappointing.

SUMMARY

Sixty patients with Wilson's disease have been studied by means of computerized cranial tomography (CT). The findings are described and analysed with particular reference to their value, both diagnostic and prognostic, in the management of this disease.

The commonest abnormalities were ventricular dilation, 73 per cent; cortical atrophy, 63 per cent; brain-stem atrophy, 55 per cent. Characteristic hypodense areas in the regions of the basal ganglia were present in 45 per cent and almost invariably these were accompanied by one or more of the other CT abnormalities. This combination of findings is considered specific for Wilson's disease in the appropriate clinical context.

CT abnormalities were most common and most marked in patients with a neurological presentation, only 2 out of 40 having a normal scan. Similar changes were also demonstrated in three-quarters of the patients with an hepatic presentation and nearly half of those who were presymptomatic.

Nineteen patients were scanned on more than one occasion to assess the influence of treatment with penicillamine or triethylene tetramine on the abnormalities recorded initially. Fourteen showed basal ganglia hypodensities on first scanning and in ten of these there was a moderate to marked improvement in this abnormality in response to therapy. Corresponding with this there was considerable clinical improvement.

Despite the findings of quite severe CT abnormalities in patients with Wilson's disease, suggesting considerable loss of neurons, patients will still respond well to treatment. We conclude that although the CT examination of patients with Wilson's disease is of value both in diagnosis and management, it is of no great help in prognosis.

ACKNOWLEDGEMENTS

F.J.B.W. acknowledges the permission of the Director General of the Royal Air Forces Medical Services to participate in this study. We are both indebted to Dr Desmond Hawkins for the hospitality of the Department of Neuroradiology at Addenbrooke's Hospital and to Helena Szutowicz and her colleagues for performing the CT scans. J.M.W. wishes to thank all those physicians who referred patients with Wilson's disease; without their co-operation this study would not have been possible.

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REGIONAL CEREBRAL OXYGEN SUPPLY AND UTILIZATION IN DEMENTIA

A CLINICAL AND PHYSIOLOGICAL STUDY WITH OXYGEN-15 AND POSITRON TOMOGRAPHY

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INTRODUCTION

SINCE the pioneering work of Kety and Schmidt (1945, 1948), there have been many publications dealing with cerebral hæmodynamics, oxygen consumption and brain function in the dementias (Freyhan, Woodford and Kety, 1951; Lassen, Munck and Tottey, 1957; Lassen, Feinberg and Lane, 1960; Butler, Dastur and Perlin (1965). It is commonly agreed that there is a decline in both mean cerebral blood flow (CBF) and mean cerebral oxygen utilization ($CMRO_2$) in this condition, and that the reduction of mean cerebral oxygen uptake is roughly proportional to the degree of dementia.

As methods became available for the assessment of regional CBF (rCBF), it was noted that in some cases focal decreases in flow were observed in the frontotemporal regions (Ingvar and Gustafson, 1970; Obrist, Chivian, Cronquist and Ingvar, 1970). Assessment of regional $CMRO_2$ ($rCMRO_2$) was methodologically much more difficult because it was dependent on an isotope, oxygen-15(^{15}O), whose short half-life (2.1 min) required it be produced by a cyclotron at the site of its use. Grubb, Raichle, Gado, Eichling and Hughes (1977) published a study of CBF and $CMRO_2$ using ^{15}O in dementia, but reported no regional observations.

Regional data, as distinct from studies of mean hemispheric measurements, were therefore confined to rCBF. An underlying assumption of the rCBF studies was that it faithfully reflected cerebral oxygen metabolism in demented patients. There was theoretical support for this concept in view of the tight coupling of CBF to $CMRO_2$ in normal man, and by observations in hemispheric studies, of a roughly parallel decrease in CBF and $CMRO_2$, in dementia. However, the assumption that rCBF adequately reflected cerebral function received mixed support: certain authors found a correlation between degree of dementia and decrease in rCBF in degenerative (Alzheimer's) disease (Yamaguchi, Meyer, Yamamoto, Sakai, and Shaw, 1980), and others the reverse (Hachinski *et al.*, 1975). Regional studies have also addressed themselves to the problem of differentiating physiological varieties of dementia and correlating these with pathological or clinical classifications. The differentiation of dementia into two major groupings, degenerative and multi-infarct, by Tomlinson, Blessed and Roth, (1970), gave impetus to this line of research. The observations in these studies have been equally conflicting: Hachinski *et al.* (1975) have claimed a decrease in rCBF in mild or moderate multi-infarct but not degenerative dementia. Simard, Olesen, Paulson, Lassen and Skinhøj (1971) have suggested the opposite.

Recently, a technique using oxygen-15 and a positron emission tomograph has been described for the non-invasive measurement of rCBF, $rCMRO_2$ and regional oxygen extraction fraction (rOER) (Frackowiak, Lenzi, Jones and Heather, 1980). This has been used in the present study of demented patients. Our aim was to answer the following questions:

(1) can the degree of dementia be correlated with the rate of cerebral oxygen utilization?

(2) is there a correlation between the clinical type of dementia and patterns of rCBF and $rCMRO_2$ abnormalities?

(3) do pathophysiological patterns of rCBF, rOER and $rCMRO_2$ in demented patients point to pathogenetic mechanisms in this disease? In particular, is there any evidence that chronic ischæmic brain syndrome exists as a disease entity?

Our prospective study involved the parallel collection of clinical findings, morphological data (computerized tomography) and physiological measurements (positron tomography).

CLINICAL MATERIAL

Twenty-two demented patients, 10 males and 12 females, provide the case material from a total of 31 admitted to the study. All were recently diagnosed dements referred from neurological outpatient consultations. Selection of patients was prospective and reflected the type of patient with dementia commonly referred for neurological consultation in North-west London. This biased selection towards younger patients with less severe disease. There was no *a priori* attempt to select for clinical type except that secondary dementias other than those due to vascular disease were excluded. No patients with normal pressure hydrocephalus were studied.

Every attempt was made to exclude patients with pseudodementing states by clinical and ancillary investigations and by repeat examination after an interval of six months, when this was possible. Five patients were excluded on clinical grounds, because a diagnosis of dementia could not be substantiated; three had had previous cerebrovascular episodes (transient ischæmic attacks and stroke) with an acute confusional state or mild amnesia as the only sequelæ; one was suffering from a depressive psychosis and another from depression with a minor memory defect.

There thus remained 26 patients, 18 of whom had a repeat study six months after the first. Though the problem of co-operation of patients was the major technical limiting factor to accurate physiological measurement with positron tomography, it proved surmountable by constant attention to establishing and maintaining a close rapport with the patients. Nevertheless, 13 studies were rejected on technical grounds, 12 because of patient movement during scanning and one because of inaccurate arterial blood sampling.

As a result, there remained 22 patients and 10 repeat observations for analysis of the original 51 observations on the 31 patients initially admitted to the study.

Of the 22, 4 patients died within six months of first assessment, 3 with vascular and one with degenerative dementia. These categories are defined in Methods. Three died a sudden, presumed cardiovascular, death and one died of pneumonia. A fifth (degenerative) dement died nine months after assessment, extremely demented and in a virtual state of inanition.

Nine patients were hypertensive (2 degenerative and 7 vascular dements). Two patients were diabetic (both vascular). Two gave a history of previous polymyalgia rheumatica (one degenerative and one vascular), one of rheumatic fever in childhood (vascular), and one of a previous polyarteritis (vascular). Two patients were euthyroid as a result of replacement thyroxine treatment for hypothyroidism (both vascular). One patient had epilepsy as a manifestation of degenerative dementia. No patients were on drug therapy during investigations except for the two on thyroxine replacement.

Fourteen normal volunteers, 9 male and 5 female, mostly healthy employees of Hammersmith Hospital, provided an age-matched set of control data. They gave informed consent. They were screened for hypertension and a previous history of diabetes mellitus, ischæmic heart disease, cerebrovascular disease and other cerebral disease or trauma. Neurological examination was normal.

TABLE 1. BASELINE PHYSIOLOGICAL DATA FOR NORMAL AND DEMENTED POPULATIONS (±SD)

	Normal	*Demented*
No.	*14 (9 male, 5 female)*	*22 (10 male, 12 female)*
Hb g/100 ml	13.3±1.7	13.1±1.4
PaO$_2$ mmHg	80.9±5.2	79.7±8.4
PaCO$_2$ mmHg	40.5±2.5	38.6±3.2
Arterial oxygen content ml/100 ml	17.8±2.1	17.7±1.9
Systolic BP mmHg	138±8	148±12
Diastolic BP mmHg	80±4	86±10
Age (years)	61±8	66±9

The mean ages, hæmoglobins, PaCO$_2$, PaO$_2$, arterial blood oxygen contents and blood pressures for the normal and demented populations are shown in Table 1.

Informed consent was obtained from normal volunteers, patients, and when appropriate, closest relatives. The clinical protocol was approved by the Research Ethics Committees of the Royal Postgraduate Medical School, Hammersmith Hospital, and the National Hospital, Queen Square. Radiation doses were approved by the DHSS Administration of Radioactive Substances Advisory Committee.

METHODS

1. *Clinical Assessment*

Patients were investigated during a standard, five-day, hospital admission, the details of which are tabulated below:

Investigation protocol—five-day hospital admission

Day	*Investigation*
1	Clinical assessment
2	^{15}O positron tomography
3	Computerized tomography
4	EEG, ECG, chest and skull x-ray, blood tests
5	Lumbar puncture

(i) *Diagnostic examination.* All patients underwent routine clinical examination and investigations for the exclusion of pseudo-dementing states and secondary dementias, other than those due to cerebrovascular disease.

The demented patients were divided into a vascular (multi-infarct) and a degenerative (Alzheimer) group on the basis of the ischæmia score (Hachinski *et al.*, 1975; Harrison, Thomas, du Boulay and Marshall, 1979; Rosen, Terry, Fuld, Katzmann and Peck, 1980) and the presence of infarcts or focally enlarged sulci on computerized tomographic scans (Radue, du Boulay, Harrison and Thomas, 1978). The CT scan was used to define a subgroup of vascular dementias on the basis of a characteristic pattern of periventricular low white matter attenuation which was clinically associated with hypertension (Zeumer, Schonsky and Sturm, 1980).

(ii) *Neuropsychological examination.* A systematic method of assessing severity of intellectual decline and the pattern of higher cortical dysfunction was adopted. This was designed to be readily and uniformly applicable to dements of all grades of severity.

(a) General social impairment was assessed using the Dementia Scale (DS) of Blessed, Tomlinson and Roth (1968). Patients can score from 0 to 28 points, which covers a range from normal social functioning to complete dependence and social disintegration.

(b) General intellectual impairment, memory functions, the ability to concentrate and to solve problems were assessed by the Information Memory Concentration Test questionnaire of Blessed *et al.* (1968), supplemented by two tests of higher integrative functioning: cross-hatching from a standard matrix of random letters and a standard symbol decoding test. The Concentration Test ranges from 36 to 0, each of the two supplementary tests were scored 3 to 0, 0 implying severe disability. The scores were added on to the Concentration Test giving a final range of 42 to 0 reflecting normality through to gross failure of intellect, memory and integrative functions.

(c) A clinical assessment of regional cerebral function was also made. Standard clinical tests of language functions to assess reading, writing, comprehension, fluency, nominal abilities and spontaneity of speech were performed. These were graded as a group 0 to 3, reflecting normality to gross aphasia. The ability to construct, tested by copying and drawing simple and complex geometrical figures, was assessed together with the ability to dress. A 0 to 3 scale covered the range from normality to gross impairment. Finally, the ability to name and recognize the fingers, to perform mental arithmetic and calculations and to recognize right from left were assessed, and again graded 0 to 3 to reflect increasing dysfunction. The sum of the scores of the three groups of tests gave a Regional Function Score (RFS) from 0 to 9, representing lesser to greater degrees of cortical dysfunction.

Focal functional correlations of pathophysiological findings were obtained using the RFS. Severity of dementia was assessed by combining the DS, IMCT and RFS, with equal weighting for each, into a Combined Dementia Score (CDS), which thus took into account both generalized, focal and social aspects of the disease (Table 2).

Examination and scoring were performed in standard fashion by one of us, without prior knowledge of other data, in order to maintain uniformity.

TABLE 2. CLINICAL SCORING SCHEME (*see text* for details)

Test	*Range*	*Mild (1)*	*Moderate (2)*	*Severe (3)*
Dementia score	0–28	0–6	6.5–10.5	11–28
Information–memory–concentration test + integrative function tests	42–0	42–35	35–21	20–0
Regional function score	0–9	0–3	4–6	7–9
Combined dementia score	0–9	0–3	4–7	8–9
		Not demented	Demented	Severely demented

The combined dementia score is derived from the dementia score, the modified information–memory–concentration test and regional function score, by addition. One point is awarded for a mild disturbance, two for moderate and three for severe. Combined dementia score scoring forms the basis for classifying patients as demented or severely demented.

2. *Positron Tomography*

(i) *Technique.* The oxygen-15 steady-state technique was used to measure rCBF, rOER, and rCMRO$_2$ using positron emission tomography (Frackowiak *et al.*, 1980).

An ECAT II (EG and G Ortec Inc., Tennessee) was employed; this tomograph has a resolution of 14 × 14 mm in the transaxial plane (FWHM—full width at half maximum) and 16 mm in the axis of the plane (FWHM), (Jones, Forse, Heather and Rhodes, 1981). Emission data were collected for four standard transaxial planes, parallel to, and 2, 4, 6 and 8 cm above the orbitomeatal line. All emission data were corrected for tissue attenuation by the corresponding positron transmission scans, collected from the appropriate plane. The physiological (functional) data were calculated from the corrected emission scans using the simple mathematical model describing the relationships between cerebral and arterial ^{15}O tracer concentrations and rCBF, rOER, and rCMRO$_2$ (Frackowiak *et al.*, 1980).

Data collection in the initial phase of the study run *pari passu* with methodological development. The transmission scan, required for correction of emission data for tissue attenuation, was lengthened from one to five min during the course of the study, resulting in a marked improvement in the statistical quality of the derived functional data. The ability of the tomograph to present data in the form of images was used to identify the anatomical level of a scan plane and its orientation. This was of particular importance in follow-up, when comparisons between scans recorded six months apart were attempted. No accurate means of repositioning a patient in the tomograph is yet available. Two methods of repositioning in CT tomographs have been published recently (du Boulay, Fairbairn and Paden, 1978; Bergström *et al.*, 1981). However, the former requires expensive equipment, and the latter is cumbersome and impractical for the study of demented patients. This technical aspect limits accurate comparisons in follow-up studies.

Patients were required to lie still in the tomograph in a quiet darkened room. They were unsedated, the few on drug therapy before assessment had this stopped at least 24 h before scanning. The patients' eyes were closed or covered with eyepatches, physiological stimulation by touch and noise was kept to an absolute minimum. Arterial blood sampling during $C^{15}O_2$ and $^{15}O_2$ inhalation was performed by arterial puncture through pre-anæsthetized skin (bupivicaine plain 0.5 per cent). Arterial blood gases were measured in duplicate (ABL-1-Radiometer, Copenhagen); hæmoglobin was measured colorimetrically in triplicate.

(ii) *Methods of data analysis.* Functional data were analysed numerically in three ways:

(a) the best available approximation to absolute grey matter rCBF, rOER and $rCMRO_2$ were measured in the orbitomeatal line + 4 cm plane from the temporal pole/insula complex of cortex. Circular regions of interest (ROI) containing 41 picture elements and of area 2.5 cm^2 were used for making measurements. In an attempt to sample as homogenous a piece of grey tissue as the resolution of the tomograph allowed the highest mean value of $rCMRO_2$, with the smallest standard deviation, was recorded. The co-ordinates of this sampled region were then used to make rOER and rCBF measurements from the same site. Representative white matter rCBF, rOER and $rCMRO_2$ were measured from the orbitomeatal line + 6 cm plane (level of centrum semiovale) in similar fashion;

(b) regional profile measurements were obtained using large, standard, square regions of interest of 81 pixels (5 cm^2) sited anatomically (fig. 1). Ten anatomical regions, five in each hemisphere, were used in the orbitomeatal line + 4 cm plane (frontal, temporal, basal ganglia, parietal, occipital). A further ten were sited in the orbitomeatal line + 6 cm plane (frontal, fronto-parietal, parietal, occipital, calcarine). These regional measurements represent indices of rCBF, rOER and $rCMRO_2$ rather than absolute values, because the sampled volumes of tissue contain mixtures of unknown proportions of cortex and white matter. This limitation is imposed by the finite spatial resolution of the tomograph and the associated partial volume effect (Hoffman, Huang and Phelps, 1979);

(c) an index of mean cerebral or mean hemispheric CBF, OER and $CMRO_2$ can be derived by averaging the values for the twenty 5 cm^2 regions of interest from the orbitomeatal line + 4 cm and orbitomeatal line + 6 cm planes (*see* fig. 1).

3. *Computerized Tomography*

Conventional unenhanced computerized tomographic scanning was performed using an EMI 5005 General Purpose Scanner. Scanning time was 40 s/plane. The images were displayed on a 160 × 160 pixel matrix with a pixel size of 0.75 mm. The slice thickness (axial) was 13 mm (FWHM). Scans were recorded in 1-cm steps parallel to, and starting from, the orbitomeatal line, to the top of the brain.

The scans were analysed from images on x-ray photographic film, without knowledge of the patients' clinical or physiological details. The following features were assessed:

(a) infarcts or focal dilatations of the subarachnoid space;
(b) low attenuation of periventricular white matter;
(c) generalized ventricular enlargement including measurement of Evans' index and widest third ventricular dimensions;
(d) generalized cortical atrophy;
(e) visibility of temporal horns.

RESULTS

1. *Pathogenesis: Clinical Classification*

The 22 demented patients were classified as 'degenerative' or 'vascular' on the basis of the ischæmia score and clinical examination, supplemented by CT scanning.

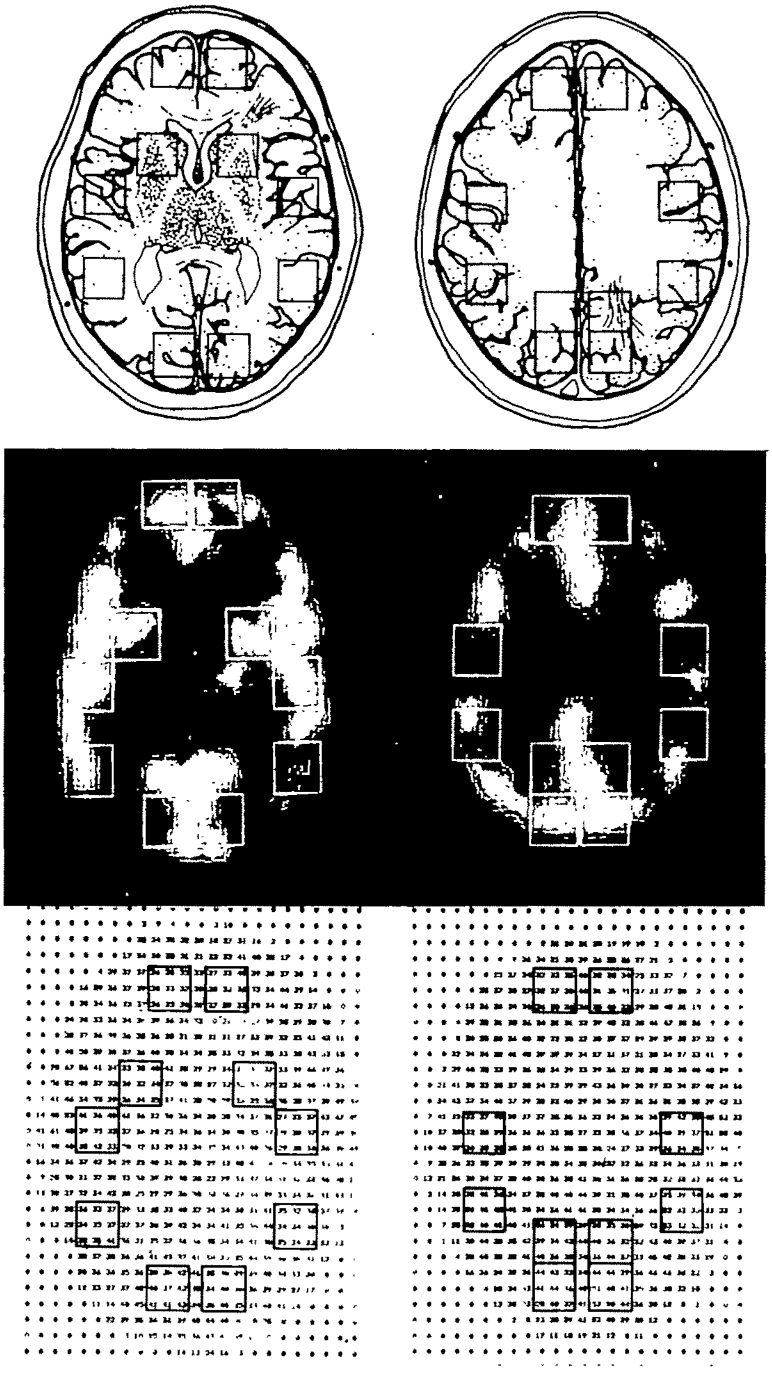

FIG. 1. Data analysis. The figure shows 5 cm^2 regions of interest containing 81 pixels, sited in a standard, anatomically based array. In the top row is an anatomical diagram for reference, the middle row shows the corresponding functional (positron) scans and the bottom row the data matrix.

Table 3 shows the ischæmia scores, CT scan findings and final classification of the 22 patients.

An ischæmia score of less than 6 correlates with an absence of focal infarcts, large focal CSF space pools in the cortical sulci and low attenuation of white matter. Two patients (Nos. 85 and 137) had low ischæmia scores with a CT scan suggestive of focal disease. Patient 85 also had low white matter attenuation and hypertension and was therefore classified as vascular (V_B—*see* Table 3). Patient 137 had an enlarged right frontal sulcal pool and a questionable left cingulate one; in all other respects the disease was of degenerative type. Two patients with ischæmia scores above 8 had no evidence of focal structural disease on CT scanning. (Nos. 32 and 43), both were classified vascular because of the typical clinical picture. Patient 43 also had a multi-infarct dementia at autopsy. Patient 37/144, with severe dementia, had frontal periventricular low attenuation, but no hypertension or any other features of multiple infarction; her ischæmia score was 3. One patient had a completely normal CT scan (No. 82/176).

TABLE 3. CLASSIFICATION OF DEMENTS INTO VASCULAR AND DEGENERATIVE TYPES MADE ON THE BASIS OF THE ISCHÆMIA SCORE SUPPLEMENTED BY CT FINDINGS

		CT scan findings					
Patient No.	*Ischæmia score*	*Infarcts/focal sulcal pools*	*Generalized attenuation of periventricular low white matter*	*Ventricular enlargement*	*Generalized cortical atrophy*	*Temporal horn*	*Classifications*
63/153	8	++		+	+	+	V
68	10	++		+	++	+	V
122/199	8	+		+			V
118/209	9	+	+	+		+	V_B
67/159	15	+	++				V_B
136	8		+	++			V_B
32	8			+	+		V
43	10			+	+	+	V
85	3	+	+	++		+	V_B
24/135	4			+	++		D
74	1			+	+		D
75/171	1			+		+	D
79	1			+			D
82/176	1						D
84	1			+	+		D
100/180	4			+	+		D
103/170	2			+	+	+	D
134	3				+		D
143	5			+	+	+	D
200	2			+	+	+	D
37/144	3			++	++	+	D
137	2	+		+	+		D

V = vascular. D = degenerative. V_B = 'Binswanger'. + = present. ++ = severe.

Consequently, 13 patients were classified as degenerative and 9 as vascular, of which 4 had diffuse low white matter attenuation and hypertension. Six degenerative dements and 4 vascular were restudied. There were therefore 19 observations in degenerative dementia and 13 in vascular (7 multi-infarct and 6 vascular with hypertension and diffuse low white matter attenuation). For group comparisons, the 22 first observations only were used; the 10 repeat observations are analysed separately (*see* (7) Sequential Studies). In the 3 cases where biopsy or autopsy evidence was available, the clinical classification was confirmed (one multi-infarct, 2 degenerative). The mean age of the degenerative group was 65 ± 7 years, and the vascular group 66 ± 11 years.

2. *Severity*

Patients were classified according to the Combined Dementia Score (CDS) described in Methods, into demented (CDS = 4 to 7) or severely demented (CDS = 8 to 9). All 5 of the patients from the original group, who were not considered demented after clinical evaluation, scored three or less on the CDS. Of the 10 repeat studies, 8 showed an increase in the CDS, though only 2 moved from demented to severely demented groups, and 2, both severely demented, had the same score on both occasions. Table 4 classifies patients and studies according to severity and pathogenesis.

TABLE 4. TABLE SHOWING NO. OF PATIENTS AND REPEAT OBSERVATIONS IN GROUPS, CLASSIFIED BY SEVERITY AND CLINICALLY DETERMINED PATHOGENESIS

	Degenerative		*Vascular*	
Severity	*Patients*	*Repeat studies*	*Patients*	*Repeat studies*
Demented (CDS 4–7)	7	3	4 V = 2 V_B = 2	2 V = 0 V_B = 2
Severely demented (CDS 8–9)	6	3	5 V = 3 V_B = 2	2 V = 2 V_B = 0
Total	13	6	9	4

CDS = Combined dementia score. V = vascular. V_B = 'Binswanger'.

3. *Grey and White Matter rCBF, rOER and rCMRO$_2$*

Representative grey and white matter rCBF, rOER and rCMRO$_2$ were measured as described in Methods. The values in dements are compared with the age-matched controls in Table 5. A parallel fall of about 30 per cent in rCBF and rCMRO$_2$ occurs for grey matter and a slightly lower fall of 23 per cent is seen in the white matter of the demented group as a whole. The oxygen extraction ratio does not change significantly, suggesting that rCBF and rCMRO$_2$ remain coupled.

TABLE 5. ABSOLUTE VALUES FOR REPRESENTATIVE GREY AND WHITE MATTER rCBF, rOER AND rCMRO$_2$ IN NORMALS AND DEMENTS

	Grey matter			*White matter*		
	rCBF ml/100 ml/min	*rOER*	*rCMRO$_2$ ml O$_2$/100 ml/min*	*rCBF ml/100 ml/min*	*rOER*	*rCMRO$_2$ ml O$_2$/100 ml/min*
Normal	50.9	0.52	4.67	21.1	0.49	1.83
n = 14	±8.7	±0.08	±0.64	±2.5	±0.06	±0.23
Demented	35.7[2]	0.54	3.33[2]	16.3[1]	0.52	1.40[2]
n = 22	±8.9	±0.08	±0.48	±6.0	±0.10	±0.33
% change	−30	+4	−29	−23	+6	−23

Results are shown ±1 SD. There was no significant difference in the rOER between the two groups. [1] = $P < 0.01$. [2] = $P < 0.001$.

Table 6 shows the relationship between blood flow, oxygen consumption and severity of dementia. A progressive coupled fall in both occurs, with a decline of 20 per cent from control in dements, and over 35 per cent in severe dementia. There is a negative correlation between the Combined Dementia Score (CDS) and rCMRO$_2$ which reaches statistical significance ($n = 22$; $r = -0.74$; $P = < 0.001$). There is a similar negative correlation between rCBF and the CDS ($n = 22$; $r = -0.70$; $P = < 0.001$).

Table 6 shows the absence of a relationship between oxygen supply (rCBF) and demand (rCMRO$_2$), and clinically determined pathogenesis. Both the vascular group and the degenerative show a coupled depression of rCBF and rCMRO$_2$ in

TABLE 6. ABSOLUTE VALUES FOR REPRESENTATIVE GREY MATTER rCBF, rOER AND rCMRO$_2$ TABULATED AS A FUNCTION OF CLINICALLY DETERMINED PATHOGENESIS AND SEVERITY OF DEMENTIA, COMPARED TO NORMALS

	rCBF-grey ml/100 ml/min	*rOER-grey*	*rCMRO$_2$-grey ml O$_2$/100 ml/min*
Normal	50.9	0.52	4.67
n = 14	±8.7	±0.08	±0.64
Dementia	40.3[1]	0.52	3.79[2]
n = 11	±9.8	±0.08	±0.56
	−21%*	0	−19%
Severe dementia	31.1[2]	0.57	3.02[2]
n = 11	±4.9	±0.08	±0.40
	−39%	+10%	−35%
Degenerative	35.0[2]	0.54	3.40[2]
n = 13	±6.9	±0.06	±0.39
	−31%*	+4%	−27%
Vascular	36.7[1]	0.54	3.35[2]
n = 9	±11.7	±0.11	±0.56
	−28%	+4%	−28%

Results are shown ±1 SD. * = percentage change from normal mean. [1] = $P < 0.01$. [2] = $P < 0.001$.

grey matter, which is similar in degree to the demented group as a whole. There is no evidence for ongoing ischæmia in the vascular patients in that no significant elevation of rOER is observed.

In summary, a negative correlation has been demonstrated between the absolute level of grey matter rCMRO$_2$ and severity of dementia, which is largely paralleled by the rCBF. No correlation between oxygen utilization, flow or a mismatch of these normally tightly coupled variables and the presumed pathogenesis, has been shown.

4. *Mean Hemispheric CBF, OER and CMRO$_2$*

Mean values for CBF, OER and CMRO$_2$ in each hemisphere are grouped according to pathogenesis and severity and presented in Table 7. Normal values are shown for comparison. There was no significant difference between right and left hemispheres, both being depressed in terms of oxygen supply and utilization to the same extent, though the right hemisphere was always depressed a few percentage points more than the left in the severe dements.

5. *Regional Variation in CBF and CMRO$_2$*

Six key cerebral areas have been analysed by the method of 5 cm^2 anatomically-sited square ROIs and these areas are labelled in italics to denote their anatomical sites of origin: *frontal*-mean of two frontal ROI in the orbitomeatal plane + 4 cm and two in the orbitomeatal plane + 6 cm; *temporal*-mean of two in the orbitomeatal

TABLE 7. MEAN WHOLE BRAIN CBF, OER AND CMRO$_2$ TABULATED AS A FUNCTION OF SEVERITY AND CLINICALLY DETERMINED ÆTIOLOGY OF DEMENTIA AND COMPARED WITH NORMALS

	CBF *ml/100 ml/min*	*OER*	*CMRO$_2$* *ml O$_2$/100 ml/min*
Normal	39.6	0.55	3.80
n = 14	±5.0	±0.08	±0.5
Dementia	33.4	0.54	3.15^2
n = 11	±7.6	±0.07	±0.3
	$-16\%^*$	−2%	−17%
Severe dementia	26.9^2	0.57	2.60^2
n = 11	±3.6	±0.09	±0.26
	−32%	+4%	−32%
Degenerative	29.6^2	0.56	2.87^2
n = 13	±5.6	±0.07	±0.40
	−25%	+2%	−24%
Vascular	30.9^2	0.55	2.89^2
n = 9	±8.4	±0.10	±0.40
	−22%	0%	−24%

Results are shown ±1 SD. $^1 = P < 0.01$. $^2 = P < 0.001$.

plane + 4 cm; *fronto-parietal*-mean of two in the orbitomeatal plane + 6 cm; *basal ganglia*-mean of two in the orbitomeatal plane + 4 cm; *parietal*-mean of two from the orbitomeatal plane + 4 cm and two from the orbitomeatal plane + 6 cm; *occipital*-mean of two from the orbitomeatal plane + 6 cm. There is a uniform, coupled decline of CBF and CMRO$_2$ between normal and demented groups for each of the regions studied.

TABLE 8. REGIONAL CMRO$_2$ AND CBF FROM SIX KEY CEREBRAL AREAS IN THE DEMENTED GROUP AS A WHOLE AND COMPARED WITH NORMALS

	Region	*Normal* *n* = *14*	*Dements* *n* = *22*	*% change*
rCMRO$_2$				
ml O$_2$/100 ml/min	Frontal	3.55±0.53	2.71±0.57[2]	−24
	Temporal	3.76±0.35	2.88±0.41[2]	−23
	Fronto-parietal	3.76±0.73	2.83±0.51[2]	−25
	Basal ganglion	4.04±0.56	3.11±0.54[2]	−23
	Parietal	3.50±0.51	2.49±0.60[2]	−29
	Occipital	4.06±0.69	3.29±0.57[1]	−19
rCBF				
ml/100 ml/min	Frontal	38.3±4.1	29.9±8.8[2]	−22
	Temporal	40.2±6.2	31.4±8.1[2]	−22
	Fronto-parietal	40.3±6.0	30.4±8.1[2]	−25
	Basal ganglion	43.3±8.2	34.0±9.5[1]	−21
	Parietal	36.0±3.8	24.2±6.5[2]	−33
	Occipital	40.9±6.4	33.1±7.7[1]	−19

Results are shown ±1 SD. [1] = $P < 0.01$. [2] = $P < 0.001$.

The percentage changes in rCBF and rCMRO$_2$ are tabulated in Table 8, which show that there is a differential perturbation of function between the regions. The *frontal*, *temporal*, *fronto-parietal* and *basal ganglia* regions, all show a depression of 20 to 25 per cent in rCBF and rCMRO$_2$. The *occipital* region is least affected with a depression of 19 per cent whilst the *parietal* is most affected with a fall of 29 to 33 per cent.

In Table 9, the regional CMRO$_2$ data is broken down according to type and severity of dementia. In the milder forms of both vascular and degenerative dementia, the depression in *parietal* rCMRO$_2$ is the most severe, being of the order 23 to 25 per cent. In mild degenerative dementia there is a similar fall in *temporal* rCMRO$_2$. The severe degenerative dements show a very marked depression of 40 per cent below normal in *frontal* and *parietal* rCMRO$_2$ (an example is shown in fig. 2). The selective effect on the *frontal* lobes is not seen in the vascular dements. By contrast, the *occipital* regions in the mild degenerative group are relatively spared, the rCMRO$_2$ depression being only 11 per cent. In the severe vascular group, the

TABLE 9. rCMRO$_2$ FROM FOUR KEY CEREBRAL AREAS TABULATED AS A FUNCTION OF SEVERITY AND CLINICALLY DETERMINED ÆTIOLOGY AND COMPARED WITH NORMALS

		Frontal CMRO$_2$ ml O$_2$/100 ml/min	*Temporal CMRO$_2$ ml O$_2$/100 ml/min*	*Parietal CMRO$_2$ ml O$_2$/100 ml/min*	*Occipital CMRO$_2$ ml O$_2$/100 ml/min*
Normal n = 14		3.55 ±0.53	3.76 ±0.35	3.50 ±0.51	4.06 ±0.69
Degenerative n = 13	Demented n = 7	3.02^{1} ±0.28 −15%*	2.88^{2} ±0.27 −23%	2.64^{2} ±0.33 −25%	3.61 ±0.65 −11%
	Severely demented n = 6	2.14^{2} ±0.42 −40%	2.77^{2} ±0.35 −26%	2.09^{2} ±0.34 −40%	3.07^{1} ±0.56 −24%
Vascular n = 9	Demented n = 4	3.35 ±0.43 −6%	3.33 ±0.60 −11%	2.68 ±0.62 −23%	3.34 ±0.45 −18%
	Severely demented n = 5	2.61^{2} ±0.24 −26%	2.64^{2} ±0.29 −30%	2.19^{2} ±0.26 −37%	3.07^{1} ±0.46 −24%

Results are shown ±1 SD. * = percentage change from normal. $^1 = P < 0.01$. $^2 = P < 0.001$.

principal effect in terms of oxygen utilization occurs in the *parietal* regions where rCMRO$_2$ depression is 10 per cent greater than in the *frontal* or *occipital* and 7 per cent more than in the *temporal*. The effects on rCBF parallel those in rCMRO$_2$ exactly (*see* fig. 2).

6. *Functional Correlations*

An attempt was made to find correlations between clinically-elicited functional abnormalities and regional alterations in rCMRO$_2$. Although a general trend for the rCMRO$_2$ to fall with increasing functional disability was observed for patients with aphasia and apraxia, this was not specific to any region, but reflected the severity of the dementia in general. For example, a decrease in rCMRO$_2$ from 2.73 ± 0.60 ml/100 ml/min, in patients without aphasia, to 2.30 ± 0.48 ml O$_2$/100 ml/min in patients with severe aphasia occurred in the left *temporal* region. However, the right *temporal* rCMRO$_2$ was also depressed in severe aphasics at 2.36 ± 0.68 ml O$_2$/100 ml/min. Furthermore, the normal population had a *temporal* rCMRO$_2$ of 3.71 ± 0.42 ml O$_2$/100 ml/min. A similar analysis from the *parietal* regions showed no specific correlation with apraxic difficulties.

7. *Sequential Studies*

Ten quantitative follow-up studies were performed. Eight showed progression as judged by an increase in the CDS; however, only 2 changed group from demented to severely demented. Two patients, both severely demented (CDS 8 and 9) initially, showed no change in the degree of severity.

The 2 patients with change from demented to severely demented showed an absolute fall in mean cerebral CMRO$_2$ as well as in rCMRO$_2$ for *frontal* and *parietal* regions. Overall, the 10 patients showed no significant mean $CMRO_2$ change (+2 per cent) or regional *frontal* (−4 per cent) or *parietal* (+4 per cent) change. The frontal/occipital ratio fell by 11 per cent. This implies a more marked *frontal* depression than averaging $rCMRO_2$ for all the *frontal* regions suggests. This may be due to the different starting points in terms of severity between the 10 patients, and also to the relatively small severity changes over the short follow-up period.

The clinical and analytical data for all the individual patients are available from the authors on request.

DISCUSSION

A. *Clinical and Physiological Findings*

1. *Classification of dementia.* The distinction between degenerative and vascular (multi-infarct) dementia can be made clinically with reasonable reliability. In the present study, the constellation of clinical features encompassed by the ischæmia score of Hachinski *et al.* (1975) has been used because pathological evidence (Rosen *et al.*, 1980) and ancillary clinical evidence (Harrison *et al.*, 1979) support its discriminant value. The patients fell into two distinct groups on the basis of this score. CT scanning was used to provide confirmatory, *in vivo*, morphological data, and this indeed tended to support the clinical classification in the majority of cases. Two patients with high ischæmia scores had no evidence of infarction on CT scanning, an observation already reported by Radue *et al.* (1978). It may be that in some cases diffuse, primarily cortical, ischæmic softening may not result in an observable change in the attenuation characteristics of the cerebral tissue.

A particular syndrome of hypertension, focal neurological signs and low attenuation of white matter on CT scanning, has been defined (Zeumer *et al.*, 1980) and linked to Binswanger's chronic subcortical leukoencephalopathy. Four such patients were studied of which one had a low ischæmia score. In this case the ischæmia score classification was over-ridden and the patient was classified as a dement of predominantly vascular origin. The pathological evidence for regarding Binswanger's dementia as a type of multi-infarct dementia has recently been described by De Reuck, Crevits, De Coster, Sieben and van der Ercken (1980). No attempt was made to differentiate a clinical grouping corresponding to the mixed vascular and degenerative patients of Tomlinson *et al.* (1970).

The large proportion of vascular patients in the study reflected a selection bias imposed by drawing the patients from neurological clinics. The patients as a group therefore tended to be younger and less severely demented than those from geriatric or psychiatric institutions. The degenerative patients below the age of 60 years would have previously been classified as pre-senile in contrast to the over 60-years senile dements. This distinction has not been made in this study, in keeping with modern concepts of pathology of the Alzheimer-type degenerative dementias (Constantinidis, 1978).

2. *Severity of dementia.* Despite the observations of Sokoloff (1966) of no significant change in perfusion between young and elderly normals, the majority of reports have found a decrease (Kety, 1956), often ascribed to the less selected nature of the majority of normal control populations. The normal volunteers providing our control data, though active and free of obvious past or present disease, were not selected as rigorously as in the study by Sokoloff. Therefore the demented patients have been compared with an age-matched control population. A study of the normal physiological changes in CBF and CMRO$_2$ with ageing will be the subject of a separate report.

An objective measure of severity in dementia is difficult. Various scoring procedures have been tried (Fuld, 1978). The method employed here used two scoring systems evolved by Blessed *et al.* (1968) for their correlative studies of pre-mortem clinical findings and post-mortem pathological observations in dementia. These tests, the dementia score and the information-memory-concentration test, were supplemented by an assessment of higher cerebral function obtained by neurological examination at the bedside. In this way an over-all assessment of social, integrative and regional function was obtained which served as a basis for classification into demented and severely demented groups.

Some experimental evidence exists for the validity of such a scoring system in the assessment of disease severity. Fuld (1978) demonstrated a 0.97 concordance rate in a test-retest reproducibility study of the information-memory-concentration test questionnaire. This test has also been shown to correlate with the plaque counts in Alzheimer's disease (Blessed *et al.*, 1968). In the patients followed up in this series, clinical progression was always mirrored by an increase in the combined dementia score.

3. *Regional flow metabolism relationships.* When regional measurement of CBF became a practical possibility, studies of rCBF alone were assumed to reflect cerebral energy metabolism because of the previously noted coupled decline in CBF and CMRO$_2$ in hemispheric measurements. Grubb *et al.* (1977) made direct measurements of CBF and CMRO$_2$ by an intracarotid technique utilizing ^{15}O. Regional data was not quoted in their communication which used external collimated probes for tracer detection after bolus injection. Their data also showed a coupled decline in CBF (37 per cent) and CMRO$_2$ (33 per cent) in patients with 'cerebral atrophy'.

A pioneering glimpse into regional CBF and CMRO$_2$ relationships in dementia was provided in qualitative fashion by Lenzi *et al.* (1977, 1980). They used ^{15}O administered by continuous inhalation, and an Anger gamma camera to image flow and 'metabolism' in two demented patients, in whom they demonstrated a coupled depression in the frontal lobes.

We have now extended the steady-state ^{15}O technique to quantitative tomographic, regional measurement of rCBF, rOER and rCMRO$_2$ by the use of a positron tomograph.

No focal disturbances of the oxygen extraction ratio were observed in dements of degenerative or vascular ætiology. The assumption that rCBF reflects cerebral oxygen utilization in dementia is thus generally true. Focal defects of oxygen extraction are observed in and around recent cerebral infarctions (Frackowiak *et al.*, 1981; Baron *et al.*, 1978); however, in most cases, recoupling of flow to oxygen demand occurs later (Baron *et al.*, 1979). Therefore focal defects in oxygen extraction might be expected to occur only during focal ischæmic exacerbations of dementia of vascular origin. We have observed no such defects.

The reports by certain authors (O'Brien and Mallet, 1970; Hachinski *et al.*, 1975; Simard *et al.*, 1971) of a difference in rCBF between degenerative and vascular dementias in the early stages of disease requires further comment. O'Brien and Mallett (1970) suggested that the primary decline in perfusion they observed in vascular dementia might itself cause ischæmic cell death. An equally plausible explanation of the discrepancies resides in the ^{133}Xe technique itself. This measures flow in superficial perfused cortex viewed by a detector. If infarcted cortex occupies the field of view under a detector, a low flow may be recorded if some perfusion persists. Conversely, a high flow may be recorded if a surviving perfused region lies adjacent to a grossly underperfused infarcted region. The washout from normal brain may swamp the slow washout component from the infarct and give rise to an artificially high result.

The ^{15}O method does not suffer from this source of error. The data presented here show no mismatch between flow and metabolic rate in mild or moderate vascular and degenerative dements.

4. *Chronic cerebral ischæmia.* Hemispheric studies have shown a coupled reduction in CBF and CMRO$_2$ in dementia, a result also obtained in our study. If chronic cerebral hypoperfusion were a primary event resulting in a secondary fall in CMRO$_2$, an increase in oxygen extraction would be expected, at least in the early stages of the illness. No significant elevation of directly-measured OER has been found in mild or severe dementia of vascular or degenerative type. This finding adds further support to the hypothesis of Hachinski, Lassen and Marshall (1974) that chronic global cerebral ischæmia is not a major pathogenetic mechanism in dementia.

The coupled fall in flow and oxygen utilization implies that rCBF techniques alone are a reliable way of looking at regional cerebral function. However, it is probably invalid to extrapolate and consider rCBF measurements an adequate means of assessing the efficacy of treatments designed to improve cerebral function in the dementias. Treatments improving cerebral perfusion, that is, increasing CBF, may do so quite independently of any effect on CMRO$_2$, which may remain static, or even conceivably be depressed. Indeed, in the absence of chronic ischæmia (i.e., a raised oxygen extraction ratio), it is difficult to see how increasing perfusion could stimulate metabolism. Any therapeutically-induced increased perfusion may therefore be entirely inappropriate—a form of luxury perfusion. This reasoning suggests that rCMRO$_2$ measurement is required for an objective assessment of the response of regional cerebral function to therapy in dementia. (*British Medical Journal*, 1979).

5. *White matter*. The rCBF, rOER and rCMRO$_2$ measurements from representative grey matter demonstrate a 30 per cent fall in rCBF and rCMRO$_2$. The white matter rCBF and rCMRO$_2$ show a slightly lesser fall of 23 per cent but which like the grey, correlates with severity, but not type of dementia. Whether this decrease in white matter rCMRO$_2$ reflects a decline in axonal metabolism brought about by decreased traffic from a diseased cortex, or whether it is a result of disease in the white matter itself, destroying axons, is not certain. The latter eventuality almost certainly contributes in vascular dements, where white matter lacunar infarction is well recognized, but this does not explain the depression of similar degree in degenerative dements. In this context Naeser, Gebhardt and Levine (1980) report the interesting observation that presenile dements show lower white matter attenuation on CT scanning than an age-matched normal population.

6. *Regional abnormalities*. A number of observers have commented on disturbances of normal regional patterns ('landscapes') in dementia. Ingvar and Gustafson (1970) and Obrist *et al.* (1970) reported local decreases in flow in fronto-temporal regions. Harrison *et al.* (1979) noted that derangements of focal patterns occurred in both degenerative and multi-infarct dementia.

The *parietal* rCMRO$_2$ was most markedly depressed in early dementia of both types and in severe vascular dementia (fig. 2). The *temporal* rCMRO$_2$ was equally depressed in early degenerative dementia and also in severe dementia of both types.

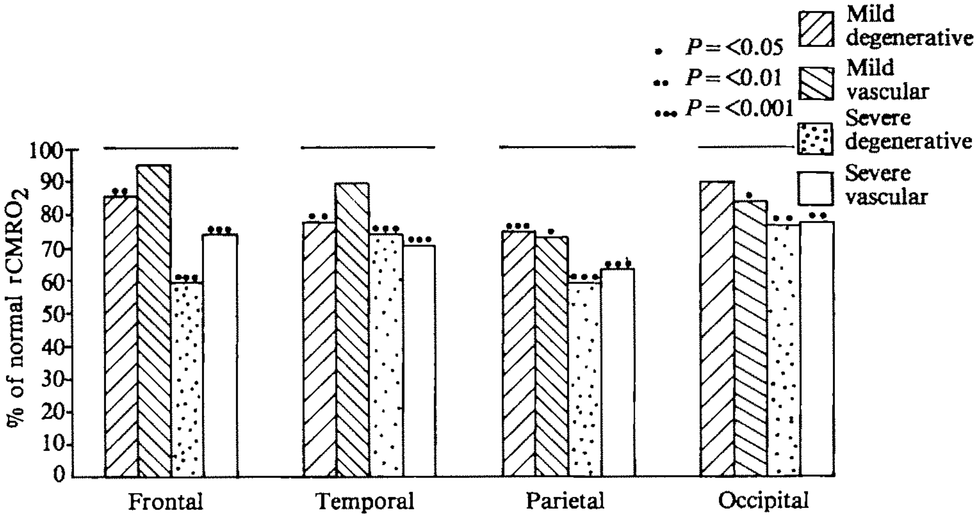

FIG. 2. Histogram showing the CMRO$_2$ for four key areas expressed as a percentage of normal and stratified to show the regional variations in function between mild and severe, vascular and degenerative groups of patients.

The *parietal* region as sampled contains some posterior temporal cortex and is probably exclusively supplied by the middle cerebral artery. Tomlinson *et al.* (1970) describe their pathological findings in 6 'arteriosclerotic', 3 'probable arteriosclerotic' and 4 mixed cases. The parietal, posterior temporal lobes or middle cerebral artery regions showed infarcts in 8 patients. In 3 others 'extensive (or enormous) numbers of cortical softenings' were described. It is likely that the frequent ischæmic damage in this area is the cause of the relatively greater depression in *parietal* $rCMRO_2$ compared to other regions in vascular dements.

The severe degenerative group show a marked depression in *frontal* $rCMRO_2$, out of proportion to the fall in *temporal* or *occipital* regions (fig. 3). Again there is a known pattern of pathological damage in degenerative (Alzheimer) disease which correlates with the pathophysiological finding. The depression in *frontal* $rCMRO_2$ is not diagnostic of severe degenerative dementia, however. Vascular dements occasionally show a drop in *frontal* $rCMRO_2$ also, presumably reflecting a randomly occurring underlying infarct. In general, however, the low *frontal* pattern is characteristic of degenerative disease. For example, 5 of the 6 severe degenerative dements had a *frontal* $rCMRO_2$ below 2.5 ml O_2/100 ml/min, whereas 4 of the 5 severe vascular dements had a *frontal* $rCMRO_2$ above this threshold. The effects of degenerative disease on the *occipital* region were less severe, all 6 severe degenerative dements had an $rCMRO_2$ above 2.5 ml O_2/100 ml/min.

7. *Focal and generalized $CMRO_2$ depression.* The focal abnormalities occur in the context of a general reduction in $CMRO_2$ in all areas, in both vascular and degenerative dementia. These disturbances may either exert a general cerebral depressant effect, or they represent superimposed exacerbations on a generalized disease process affecting all parts of the brain. In vascular dementia, the symptoms do not appear to precede ischæmic episodes, but rather accumulate with each new focal ischæmic disturbance. The mechanism for a possible generalized metabolic depression as a result of focal disease is unknown. In some vascular patients, the dispersion of ischæmic softening or infarction may be so marked that the resolving powers of the positron tomograph are insufficient to distinguish small adjacent normal and diseased parts of brain. In degenerative dementia, it is possible that disease of certain cortical areas leads to a generalized decrease in impulse traffic through associative cortex, resulting in a decrease in metabolic activity and consequently oxygen consumption in these regions.

Brains of demented people shrink. A decrease in cortical volume would lead to the sampling of proportionately more slowly metabolizing white matter by the ROI, resulting in a low $rCMRO_2$. Thus, such a fall in $rCMRO_2$ would *inter alia* reflect a real decrease in the volume of cortical cells in the standard volume of sampled brain.

8. *Binswanger's disease.* The group of patients with hypertension, focal neurological signs and low white matter attenuation on CT scanning, behaved physiologically like multi-infarct dementia. Recent pathological evidence (De Reuck, *et al.*,

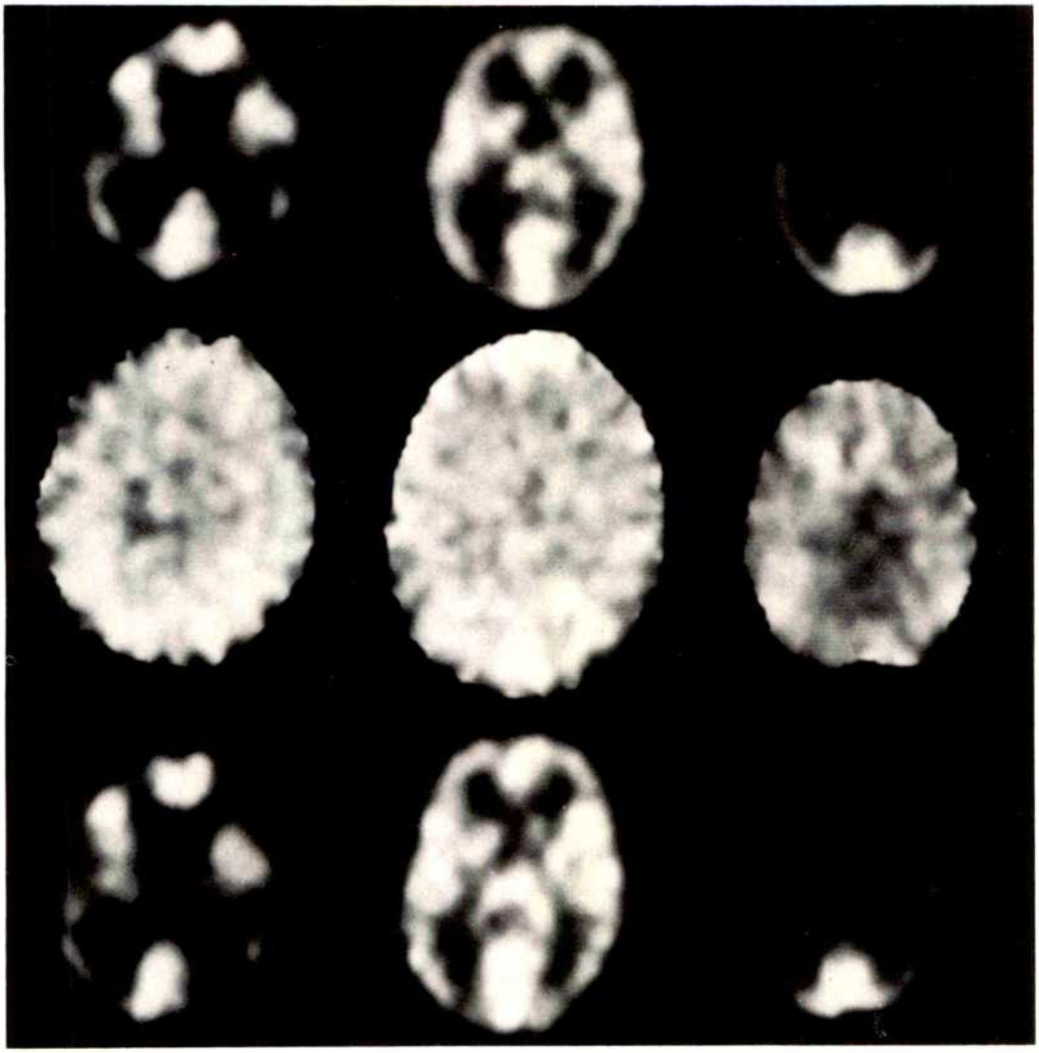

FIG. 3. Functional scans through the orbitomeatal +4 cm plane. The cerebral blood flow is shown in the top row, the oxygen extraction in the middle row and the oxygen consumption along the bottom. A scan from a normal volunteer is shown in the middle column to compare with a patient with multi-infarct dementia on the left and a patient with severe degenerative dementia on the right. Note in the multi-infarct example, which is extreme, the patchy coupled defects in cortical flow and metabolism. In the degenerative case, there is marked generalized depression in flow and oxygen utilization throughout the anterior parts of the brain and in particular in the frontal cortex. These scans should be read like conventional CT scans, with the nose pointing upwards, and the left of the head being to the left.

1980) suggests no pathological differences of note either. No significant $rCMRO_2$ or rCBF correlates of the low CT attenuation regions were seen, though the 'Binswanger' $rCMRO_2$ for white matter was lowest (1.17 ± 0.46 ml O_2/100 ml/min) when compared with other patients with vascular disease ($rCMRO_2 = 1.27 \pm 0.30$ ml O_2/100 ml/min) and degenerative disease ($rCMRO_2 = 1.43 \pm 0.37$ ml O_2/100 ml/min). This parallels the known distribution of pathology in the different groups.

B. *Methodology*

1. *Limitations imposed by tomographic resolution.* The oxygen-15 steady-state technique has been devised for making representative measurements of rCBF, rOER and $rCMRO_2$ in grey and white matter (Frackowiak *et al.*, 1980). The major limitation to absolute quantitation is the resolution of the positron tomograph, and the associated partial volume effect (Hoffman *et al.*, 1979). This results in an incomplete recovery of counts from an homogenous sampled tissue, unless its dimensions approach twice the resolution of the tomograph (i.e. 2.8 × 2.8 cm for the Hammersmith ECAT II). In the human brain, only the temporal/insular mass of cortical grey matter and the white matter of the centrum semiovale approach these dimensions, and even they contain a small proportion of white or grey matter mixed with the predominant tissue type.

Because such a wealth of regional data is potentially available from each transaxial slice of brain, methods of extracting physiologically meaningful indices of rCBF, rOER and $rCMRO_2$ within the defined limits have needed development. We have used regions of interest of large surface area (5 cm^2) to obtain local data from beyond the representative temporal/insular and centrum semiovale regions. These are sited in standard, anatomically-determined fashion to eliminate observer bias. This inevitably implies that mixtures, of unknown proportions, of cortical and immediately-underlying white matter will be included in the regions of interest (ROI).

The relationship between cerebral ^{15}O tracer concentration and CBF at equilibrium under conditions of continuous inhalation of $C^{15}O_2$ is non-linear (Jones, Chesler and Ter Pogossian, 1976). Therefore, when mixtures of tissues of different CBF are sampled, the mean equilibrium tracer concentration is weighted towards the low flow tissue components. Theoretical calculation shows that for a 50:50 grey:white mixture, such weighting results in an underestimation of CBF by up to 18 per cent. Thus the mean values using the 5 cm^2 ROI method of analysis underestimate the true mean CBF for any given mixture in absolute terms, though they continue to give a meaningful index for physiological analysis.

In calculating mean or hemispheric cerebral flow by averaging ten or twenty 5 cm^2 ROI, it is reasonable to assume that the over-all proportion of grey to white matter will reflect that of the brain as a whole (that is, approximately 50:50). The mean CBF for the 14 normals was 39.6 ml/100 ml/min. Assuming an 18 per cent underestimation due to the effect of tissue heterogeneity, the corrected CBF becomes 48.3 ml/100 ml/min. This value is marginally less than those obtained in normal subjects, using invasive techniques for measuring hemispheric blood flow: for example, CBF calculated to ten minutes of saturation or desaturation (washout) gave values (a) using the N_2O inhalation technique, 53.8 ± 12.0 ml/100 g/min in 14 normal subjects (Kety and Schmidt, 1948); (b) using the ^{85}Kr inhalation technique, 50.4 ± 4.9 ml/100 g/min in 11 normal subjects (Lassen *et al.*, 1960); and (c) using the ^{133}Xe injection with external recording technique, 49.8 ± 4.1 ml/100 g/min in 7 normal subjects (Ingvar *et al.*, 1965). O'Brien and Mallett (1970), using the non-invasive ^{133}Xe-inhalation procedure, obtained a cortical perfusion rate of 44.3 ml/100 g/min for a group of 11 normal subjects aged 40 years and over.

The mean CBF in demented patients was 30.2 ml/100 ml/min for 22 observations. Applying the same 18 per cent correction, this becomes 36.8 ml/100 ml/min for comparison with 38.6 ml/100 g/min computed from bilateral hemispheric CBF studies reported by Lassen *et al.* (1960), who used ^{85}Kr inhalation with ten minute desaturation. (A figure of 32.3 ml/100 g/min was also quoted for values obtained by extrapolation to infinity.) The ^{133}Xe inhalation technique in the hands of O'Brien and Mallett (1970) gave a mean cerebral perfusion rate of 40.1 ml/100 g/min for a group of 6 'primary neuronal' and 5 'secondary' dements of mild severity.

rCBF and rCMRO$_2$ values, using the positron tomographic technique of measurement, are expressed per 100 ml of tissue, as opposed to the values from isotope clearance techniques which are quoted per 100 g of perfused brain. A conversion from the former to the latter using the specific gravity is theoretically possible. However, as grey and white matter have different specific gravities and often mixtures are present in sampled regions, accurate conversion is not practicable. The difference between the two is, however, very small; for example, the specific gravity of grey matter is 1.050 g/ml and thus first order, direct comparisons between the values expressed in the two units are possible.

In summary, given the resolution of the tomograph and the limitations it imposes on the data, the cerebral blood flow values reported in this study bear comparison with those using more invasive techniques.

2. *Modelling limitations.* A second limitation results from an assumption in the simple model relating ^{15}O tracer distributions to oxygen extraction. The simple model assumes that the contribution from the tracer in the cerebral blood volume to the tracer signal recorded from the brain, during continuous $^{15}O_2$ inhalation is negligible. Indeed, in any volume of cerebral tissue, the cerebral blood volume is only of the order of 2 to 6 per cent. A theoretical analysis of this assumption by Lammertsma, Jones, Frackowiak and Lenzi (1981) nevertheless shows that the cerebral blood volume component systematically causes over-estimation of the OER by 20 to 30 per cent. The mean cerebral OER for normals in this study is 0.55 and for dements 0.56 which, corrected for a modelling error of 25 per cent, results in an OER of 0.41 for normals and 0.42 for dements. Given the normal 'corrected CBF' of 48.3 ml/100 ml/min, a 'corrected OER' of 0.41 and the mean arterial oxygen content of 17.8 ml O_2/100 ml/min in the normals we have studied, one can compute

a mean $CMRO_2$ of 3.52 ml O_2/100 ml/min, which compares well with the value of 3.3 ml O_2/100 g/min, quoted by Sokoloff (1966) for 26 elderly normals.

A similar computation for the dements as a group, using a 'corrected CBF' of 36.8 ml/100 ml/min, a 'corrected OER' of 0.42 and an oxygen content of 17.7 ml O_2/100 ml gives a $CMRO_2$ for dements of 2.74 ml O_2/100 ml/min. This compares with the value of 2.72 ml O_2/100 g/min quoted by Lassen *et al.* (1960) for 9 dements, and 2.7 ml O_2/100 g/min quoted by Sokoloff (1966), for 10 patients with chronic brain syndrome. These comparisons endorse the internal consistency of the results obtained by this method.

It is important to note that the two major limitations are both potentially correctable by measurement. Cerebral blood volume can be measured using ^{11}CO, and positron tomography (Phelps, Huang, Hoffman and Kuhl (1979)), for direct pixel by pixel correction of OER data. This has not been attempted in this study because it involves added radioactivity and an increase in scanning time to two hours for the patient, but the problem will be solved with the new generation of multiple slice machines now being developed. Initial clinical studies in our laboratory have shown that the cerebral blood volume correction for OER is practicable, and that the measured and predicted results concur. The resolution characteristics of tomographs depend on their design and detector efficiency. Higher resolution instruments will reduce partial volume effect, and allow more extensive regional sampling of homogenous tissues.

Because the errors introduced by the two major limitations, resolution and tracer modelling, are systematic, and do not detract from the physiological significance of the results obtained, no attempt has been made to artificially adjust results in this study by applying theoretical correction factors.

3. *Technical limitations.* Certain non-systematic errors are inherent in the method. Movement of the patient between planes, between $^{15}O_2$ and $C^{15}O_2$ scans, or between transmission and emission scans, results in major inaccuracies which invalidate the results. The maintenance of physiological equilibrium over the fifty minutes of $^{15}O_2$ and $C^{15}O_2$ inhalations is essential to the method. The short half-life of the ^{15}O isotope ($t\frac{1}{2} = 124$ s), means that changes in breathing pattern can result in fluctuations in the steady-state which will reflect in the arterial blood radioactivity. The arterial sample, required to measure the steady-state tracer concentration, must therefore be taken with the greatest of care.

When follow-up measurements are attempted, the re-siting of patients in the tomograph remains a major technical problem. If regions are to be compared, an exact congruence between scan planes at original and follow-up scanning is desirable.

Given these criticisms, it remains true that the ^{15}O steady-state technique coupled with positron tomography provides an atraumatic, virtually non-invasive, simple and repeatable method for measurement of regional oxygen supply and utilization by the brain. It involves little inconvenience to the patient, does not suffer from the disadvantages of nasal airway and of extracerebral tissue contamination which occur with other inhalation techniques, and permits accurate physical delineation of the regions studied. Further, it allows a more immediate insight into brain work by directly measuring oxygen utilization, and allowing measurement of the relationship between it and perfusion.

SUMMARY

The cerebral blood flow, oxygen extraction and oxygen utilization has been measured regionally in 22 dements, and 14 aged normal volunteers. Ten demented patients were studied twice at a six-month interval from initial measurements.

The use of a steady-state ^{15}O technique and positron tomography for measuring regional cerebral blood flow, regional oxygen extraction fraction and mean cerebral oxygen utilization is discussed. The limitations of measurements are reviewed in the light of the present results and the current state of technological development in positron emission tomography is discussed.

A decline in cerebral blood flow and mean cerebral oxygen utilization was correlated with increasing severity of dementia in both degenerative and vascular dements. The decline was coupled, both for the cerebral hemisphere as a whole and regionally. There was no increase in oxygen extraction ratio globally, and therefore no evidence to support the existence of a chronic ischæmic brain syndrome.

Focal abnormalities in oxygen utilization were observed for both vascular and degenerative groups. In the vascular group, parietal defects were the most pronounced. Individual derangements of the regional pattern varied, reflecting the different unique patterns of ischæmic damage in these patients. In the degenerative group, parietal and temporal defects were seen in the less severe group, but a profound depression in the frontal regions with relative sparing of occipital areas characterized the severe degenerative dements.

ACKNOWLEDGEMENTS

We would like to thank Mr D. D. Vonberg and the staff of the MRC Cyclotron Unit, Hammersmith Hospital, for making this study possible, and especially Mr P. Buckingham for dispensing gases. Our gratitude is also due to colleagues who kindly referred patients (Doctors R. W. Ross Russell, G. Wolfson, J. Steinert, D. J. Thomas, E. G. Gordon Smith, M. Impallomeni, Professor M. Hodkinson, Doctors N. Pride and M. J. G. Harrison), to Doctors C. Pallis and D. J. Thomas who read the paper and gave their invaluable advice, and to Professor D. K. Peters for his support. Support from an MRC Training Fellowship and a Brain Research Trust grant to R. S. J. Frackowiak is acknowledged with gratitude.

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(*Received March 3, 1981*)

Brain (1981), **104**, 779–811

EXPERIMENTAL COLD INJURY TO PERIPHERAL NERVE

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INTRODUCTION

COLD injury to the extremities was succinctly described by Hippocrates (*c*.460 BC) in travellers exposed to rigorous weather conditions. Since that time observations on cold injury have largely stemmed from the exigencies of war. The devastating effects of cold upon Napoleon's troops in the Russian and Polish campaigns were meticulously documented by Larrey (1812). He was the first to recognize that distal hypothermic injury often developed in the presence of water when temperatures were just above freezing-point. These conditions were subsequently provided in the cold wet trenches of the First World War and resulted in 85,000 cases of trench foot in the British Army alone (Dunning, 1964).

Non-freezing cold injuries in the Second World War usually followed prolonged immersion of the lower extremities in sea water (Ungley and Blackwood, 1942; Ungley, Channell and Richards, 1945). The syndrome became known as immersion foot (Greene, 1941) and at times occurred so frequently that military operations were seriously jeopardized (Buckels, Gill and Anderson, 1967). Detailed clinical studies made it clear that the principal disability resulted from a cold-induced neuropathy.

Despite the plethora of clinical material and a number of experimental studies the morphological accompaniments of non-freezing injury to nerve remain uncertain. Some investigators have demonstrated a susceptibility of large myelinated fibres to cold (Denny-Brown, Adams, Brenner and Doherty, 1945; Friedman, 1945; Basbaum, 1973; Peyronnard, Pedneault and Aguayo, 1978), but Blackwood (1944*b*) reported preferential damage to small and unmyelinated nerve fibres. In other studies no relationship has been found between nerve fibre size and susceptibility to cold damage (Large and Heinbecker, 1944; Schaumburg, Byck, Herman and Rosengart, 1967).

Vasogenic œdema has long been recognized in the hyperæmic recovery stage following cold injury (Smith, Ritchie and Dawson, 1915*a*, *b*; Webster, Woolhouse and Johnston, 1942; Ungley *et al.*, 1945). It has been suggested that œdema of nerve in hypothermia might secondarily precipitate axonal damage (Lake, 1917; Basbaum, 1973). However, breakdown of the blood-nerve barrier following cold exposure has never been convincingly demonstrated.

The aim of this study was two-fold: (a) to examine in detail the sequence of morphological changes in peripheral nerve induced by cold, using quantitative light and electron microscopic techniques and (b) to assess, using horseradish peroxidase, the permeability of endoneurial capillaries in cold-damaged nerve.

METHODS

All studies were performed on 300 to 330 g male Wistar rats. Local cooling of the sciatic nerve was achieved by application of a small cuff cooled by circulating water (fig. 1). The cuff, made from epoxy resin coated copper tubing, was shaped into a hollow semicircle with a distance of 8 mm between water inlet and outlet tubes. Circulating water temperature was recorded by thermocouples while a glass bead thermister monitored the sciatic nerve surface temperature. Stimulating and recording platinum electrodes at each end of the cuff were separated by a distance of 10 mm.

Animals were anæsthetized with intraperitoneal sodium pentobarbitone (60 mg/kg body weight) and the sciatic nerve exposed surgically at the midthigh level. The nerve was carefully positioned on the cuff immediately distal to the origin of the inferior gluteal nerve and covered by paraffin. 'Parafilm'

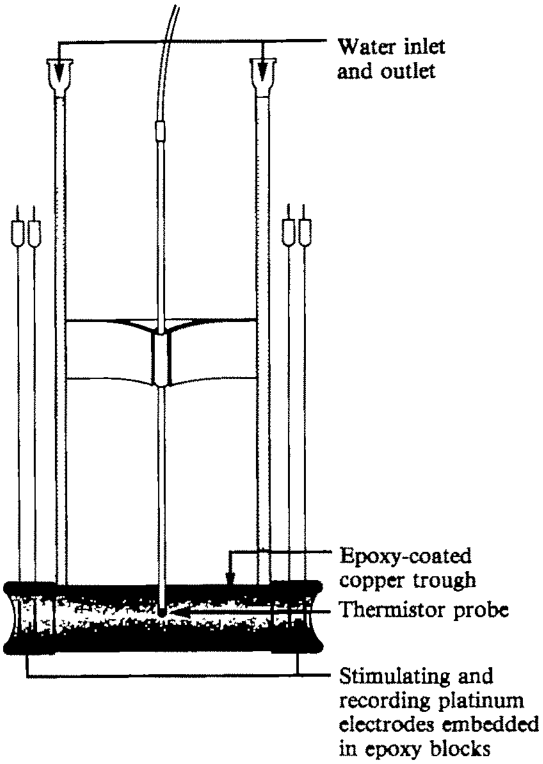
Water inlet and outlet
Epoxy-coated copper trough
Thermistor probe
Stimulating and recording platinum electrodes embedded in epoxy blocks

FIG. 1. Schematic drawing of thermode used for peripheral nerve cooling.

(American Can, Greenwich, Conn., USA) was then placed between the cuff and the underlying muscle tissue. The temperature of the inlet water was maintained at 3° C for 2 h, that of the nerve surface being 2° C higher. An electric blanket placed beneath the rat maintained a rectal temperature of 37 to 38° C. Electrophysiological studies were undertaken before, during and after nerve cooling. Supramaximal stimuli, with a duration of 0.2 ms and frequency of 0.2 Hz, were applied to the sciatic nerve through the shielded platinum electrodes, and the compound action potential recorded. Following a 2 h cooling period, the sciatic nerve was rapidly rewarmed to body temperature by circulating water at 37° C. The site of the nerve cuff was marked by a 6.0 epineurial silk suture, and muscle and skin, respectively, opposed with 4.0 silk suture and surgical clips. In each animal the contralateral sciatic nerve was used as an electrophysiological and morphological control.

Groups of 5 or 10 rats were killed either immediately following cooling or after 24 hours, 3 days, 5 days, 7 days, 2 weeks and 4 weeks. Surviving rats were examined daily to determine toe spread, placing reaction, hindlimb posture, gait, and reaction to pin-prick.

In most experiments, both sciatic nerves were fixed *in situ* for 30 min with 2 per cent glutaraldehyde in 0.1 M cacodylate buffer (pH 7.40). Using the epineurial suture as a marker of the distal cuff site, the 1 cm segment of cooled and control sciatic nerve were excised and fixation continued for one hour at room temperature. Nerves were then post-fixed in 1 per cent osmium tetroxide for 1½ h, stained with 2 per cent phenylendiamine, dehydrated in ethanol, immersed in propylene oxide and embedded in Epon 812. This tissue was sectioned at 1.5 μm and examined with a light microscope. Thin sections were subsequently stained with uranyl acetate followed by lead citrate, and examined in a Philips 300 electron microscope.

Cooled and control sciatic nerve fascicles, selected for teasing, were fixed for only 10 min in glutaraldehyde and for 1½ h in osmium tetroxide.

In a series of control experiments, rats had a cuff temperature of 37 to 38° C maintained for 2 h. These animals were then killed in pairs either immediately or after three or seven days.

The morphometric techniques used have been previously described (Pollock, Calder and Allpress, 1977; Katrak *et al.*, 1980; Nukada and Pollock, 1981). In short, measurement of 1000 to 2000 myelinated nerve fibre diameters in each nerve specimen was made with a Zeiss particle size analyser (Model TGZ-3). The density of myelinated fibres was then calculated per mm^2 of transverse fascicular area for all nerve fibres and separately for small (diameter $\leqslant 4.46$ μm) and large (diameter > 4.46 μm) myelinated fibre populations. Diameter histograms were then determined and numbers of nerve fibres calculated per whole nerve using programmed digitization.

Unmyelinated nerve fibre counts were made by examining a series of non-overlapping electron micrographs printed at a final magnification of 10 800. In each nerve unmyelinated fibres in 40 to 50 photographs (area $\geqslant 0.016$ mm^2) were counted and measured with a Zeiss TGZ-3 particle size analyser set on a linear scale. On the same photographic enlargements, numbers of Schwann cells, fibroblasts and macrophage nuclei, collagen pockets completely surrounded by Schwann cell processes and clusters of denervated Schwann cells were also determined per mm^2 of fascicular area.

The diameter distributions of myelinated and unmyelinated nerve fibres were compared with those of controls using the Kolmogorov-Smirnov two-sample test. This test is based on the agreement between the two cumulative frequency distributions with the statistic being a function of the maximum difference between the two distributions over the common diameter intervals measured. In this comparison small and large myelinated nerve fibres were also considered separately. Mean myelinated and unmyelinated nerve fibre diameters were measured and analysed statistically.

For teased nerve fibre analysis, 100 single teased fibres, each with a minimum of four internodes, were obtained from each nerve and graded descriptively (Pollock and Dyck, 1976). Teased fibre internodal length was measured using an ocular micrometer. The length and grading of abnormal internodes was compared both in terms of total nerve fibres and total internodes. In the analysis of internodes, the one-sample runs test was used to determine whether abnormal internodes were randomly distributed or clustered along particular nerve fibres.

Measurements were made on electron micrographs, using digitization of back-projected 35 mm film, of at least 100 myelinated fibres as encountered serially in X and Y traverses. The area of each axis cylinder was determined in μm^2 and major dense lines and hence number of myelin lamellæ counted. The regression analysis of logarithm (to base e) of axonal area on number of myelin lamellæ was then determined.

Tracer experiments with horseradish peroxidase (HRP) were carried out in 20 rats, (in groups of 4), at 0, 24 hours, 3, 5 and 7 days after completion of the cold injury. HRP (type II, Sigma, St. Louis) dissolved in 0.5 ml saline was injected into a jugular vein at 10 mg/100 g body weight. After 1 h, sciatic nerves were fixed *in situ* for 30 min in a solution containing 2 per cent glutaraldehyde in 0.1 M cacodylate buffer (pH 7.4). Sciatic nerves were then removed and following a further 3½ h fixation in glutaraldehyde stored in buffer overnight. Nerve segments were then frozen in isopentane, previously cooled in liquid nitrogen, and sections cut in a Harris cryomicrotome. Exogenous HRP was demonstrated using a modification of the method described by Malmgren and Olsson (1977). Tissue samples were preincubated in the dark for 30 min at room temperature in diaminobenzidine tetrahydrochloride (DAB) (20 mg of DAB in 10 ml of 0.1 cacodylate buffer, pH 5.1) and then for a further one hour in 20 mg DAB and 0.1 ml 1 per cent H_2O_2 at pH 5.1. Sections were rinsed in cacodylate buffer, and post-fixed in osmium tetroxide for Epon embedding.

The method used for determination of anterograde axonal transport was a modification of the technique described by Bray, Hubbard and Mills (1979). Under ether anæsthesia, the spinal cord was exposed by laminectomy at the level of L1 vertebra and 1 – [5^3-H] proline (specific activity 14 Ci/mmol) injected into the ventral horn with a micropipette fashioned from a glass capillary tubing (Drummond 1 μl Microcaps). A series of four pairs of 0.1 μl injections were made symmetrically in both sides of the cord at 1 mm intervals. A total of 20 μCi of 1 – [5^3-H] proline in a volume of 0.8 μl of 0.9 per cent saline was injected per animal. Four hours after ventral horn injection, local cooling of sciatic nerve to 5 or 10° C was commenced and maintained for 2 or 4 h. At the same time the contralateral sciatic nerve was ligated with a silk thread in the midthigh region. After cooling, rats were killed and the sciatic nerves and fifth lumbar roots removed. Nerves were cut into 2.5 mm segments in the cooled and ligated areas and into 5 mm segments in the proximal and distal portions. Nerve samples were counted in a Packard Tri-carb liquid scintillation spectrometer at an efficiency of 33 to 35 per cent.

RESULTS

Electrophysiological Studies

Sciatic motor nerve action potentials showed marked slowing of conduction velocity with decrease in amplitude within 1 to 3 min of the commencement of cooling and a total conduction block at 5 min. The sciatic nerve action potential invariably returned during rewarming but although a normal latency was restored within 30 to 40 min, the mean action potential amplitude recovered to only 56 per cent of normal.

Rats examined soon after nerve cooling showed only mild impairment of toe-spread on the cooled side. However, this clinical deficit slowly progressed with toe-drop and poor resistance to passive movement of the cooled leg in evidence after 24 h. By the second or third day after cooling, foot-drop was present with disturbance of gait, weak extension of the hindlimb and impairment to pin-prick. After three to seven days all animals showed evidence of severe sciatic nerve paralysis on the cold affected side. Clinical recovery began two weeks after cold injury and rapidly progressed so that after four weeks only minimal weakness remained.

Morphological Studies

Light microscopic examination of cooled nerve (figs. 2 and 3) showed severe œdema beginning after a delay of 24 h and progressing over the ensuing seven days. Œdema was first seen in the subperineurium and around endoneurial capillaries. Later it appeared to split myelin lamellæ and spread within the endoneurium. Two weeks after cold injury, nerve œdema began to decrease and it had completely resolved after four weeks. Swollen myelinated fibres, often with associated dense axoplasm, appeared 24 to 72 h after cold injury but prominent axonal degeneration and thinly myelinated fibres were not seen until five to seven days. Groups of regenerating nerve fibres were prominent two to four weeks after hypothermic injury.

Electron microscopy of sciatic nerve immediately following the cold lesion failed to reveal peripheral nerve pathology. However, some axons were distended with organelles (large membranous bodies or vesiculotubular structures) from 24 h after cooling (figs. 4 and 5) and Schwann cells often exhibited prominent peripheral vesicles (fig. 6). Three days after nerve cooling intramyelinic œdema was first noted (fig. 7). At this time only sparse axonal degeneration was present. The ultrastructural findings seven days after nerve cooling included prominent axonal degeneration (figs. 8 and 9), occasional 'naked' or thinly myelinated axons (fig. 10A and B) and clusters of regenerating myelinated fibres. In addition endothelial cells of endoneurial capillaries were swollen and their peripheral processes retracted (fig. 11).

In control normothermic experiments, no clinical, electrophysiological or morphological abnormalities were detected.

Morphometric Studies

Sciatic whole nerve area significantly increased immediately after cooling (Table 1) and subsequently continued to increase in 24 h, three, five and seven day cold groups.

TABLE 1. WHOLE SCIATIC NERVE AREA IN COLD EXPOSED RATS AND CONTROLS

Interval after cold	*Area* (mm^2)	*SD*	*No.*
Control	0.59	0.02	10
0 hours	0.66[1]	0.05	4
24 hours	0.74[2]	0.08	5
3 days	0.78[2]	0.08	4
5 days	0.80[2]	0.02	4
7 days	0.87[2]	0.10	10
2 weeks	0.83[2]	0.04	3
4 weeks	0.77[2]	0.07	3

[1] $P < 0.005$. [2] $P < 0.001$.

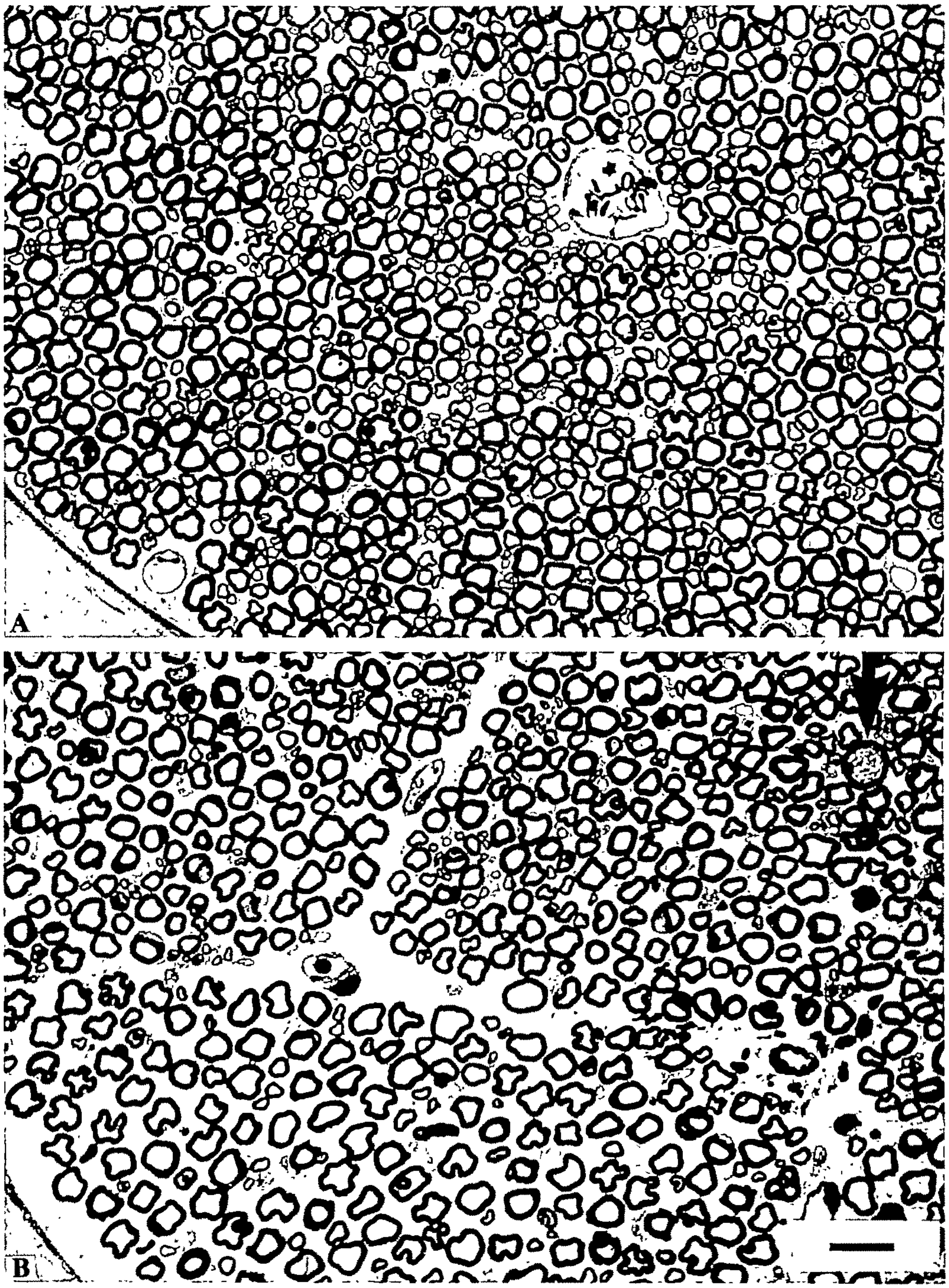

FIG. 2A, transverse section of sciatic nerve from a control rat. B, transverse section of rat sciatic nerve twenty-four hours after cold injury showing unequivocal perivascular and subperineurial œdema but only minimal endoneurial œdema. Note solitary swollen axon with dense axoplasm (arrow). Phenylenediamine staining. Bar = 20 μm.

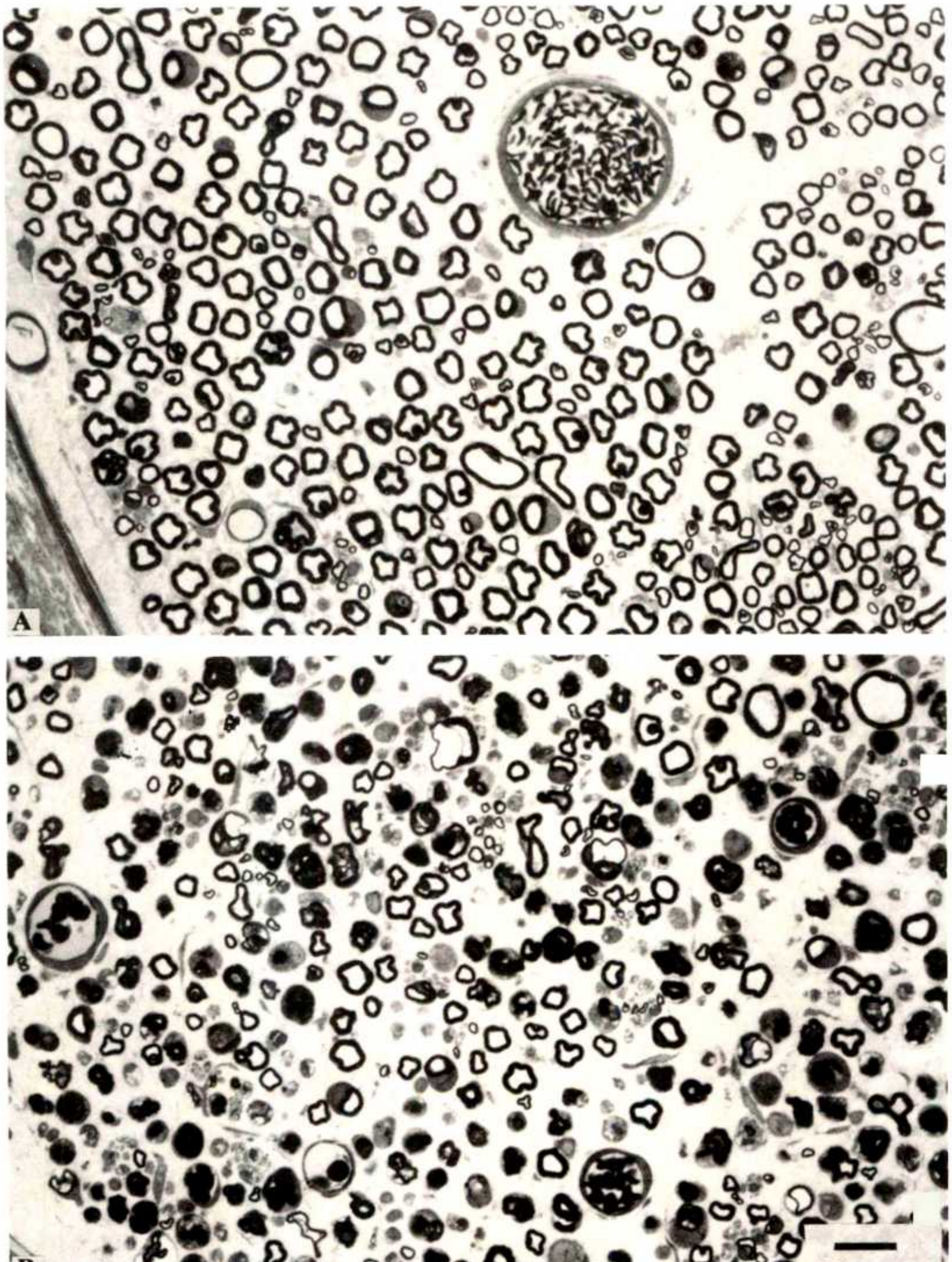

Fig. 3A, transverse section of rat sciatic nerve three days after cold injury showing severe endoneurial œdema. B, rat sciatic nerve seven days after cold injury showing prominent axonal degeneration, myelin splitting and marked œdema. Phenylenediamine staining. Bar = $20\ \mu m$.

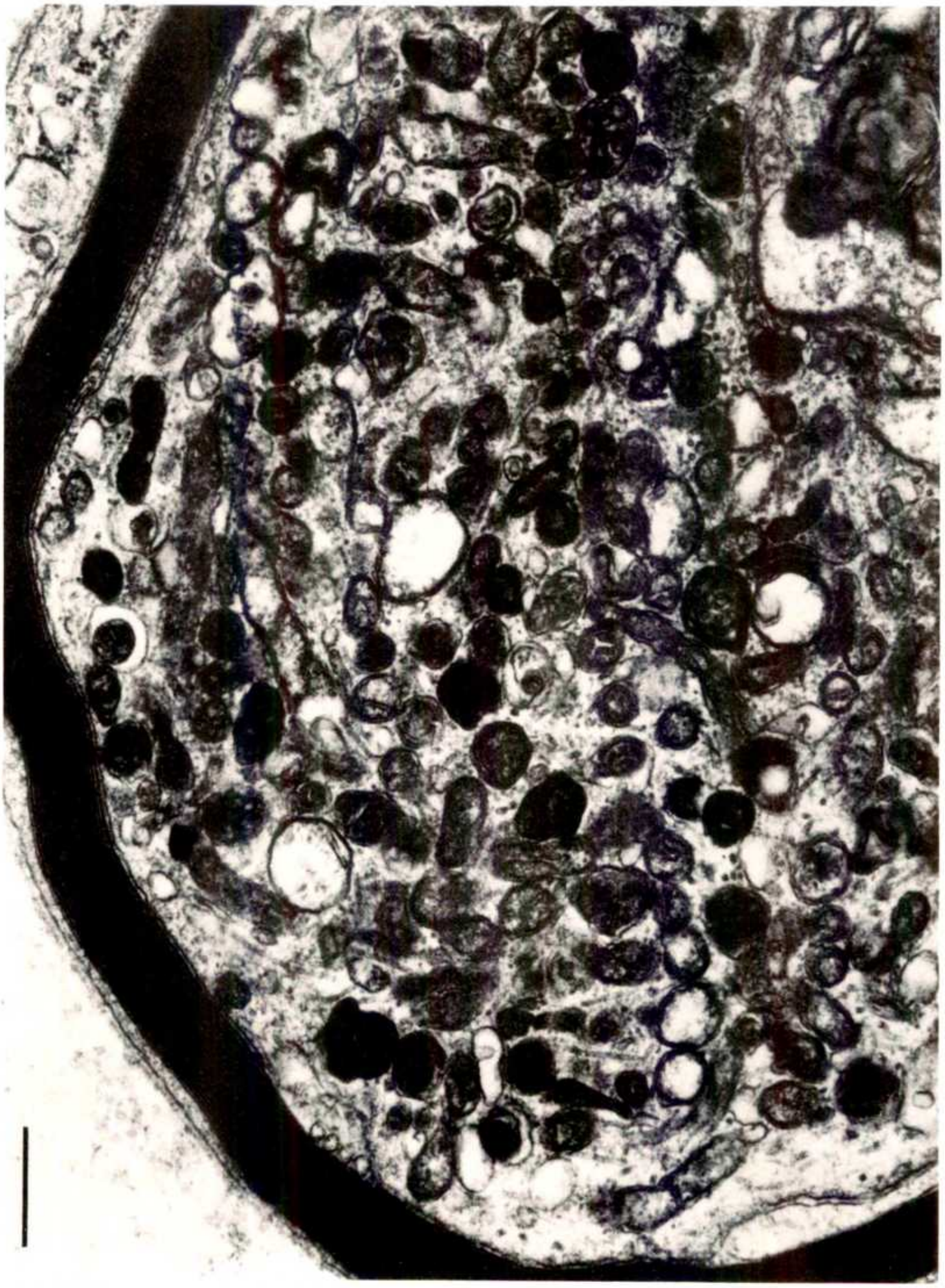

FIG. 4. Electron micrograph of transverse section from rat sciatic nerve three days after cold injury. The swollen axoplasm is filled with large membranous bodies. Bar = 0.5 μm.

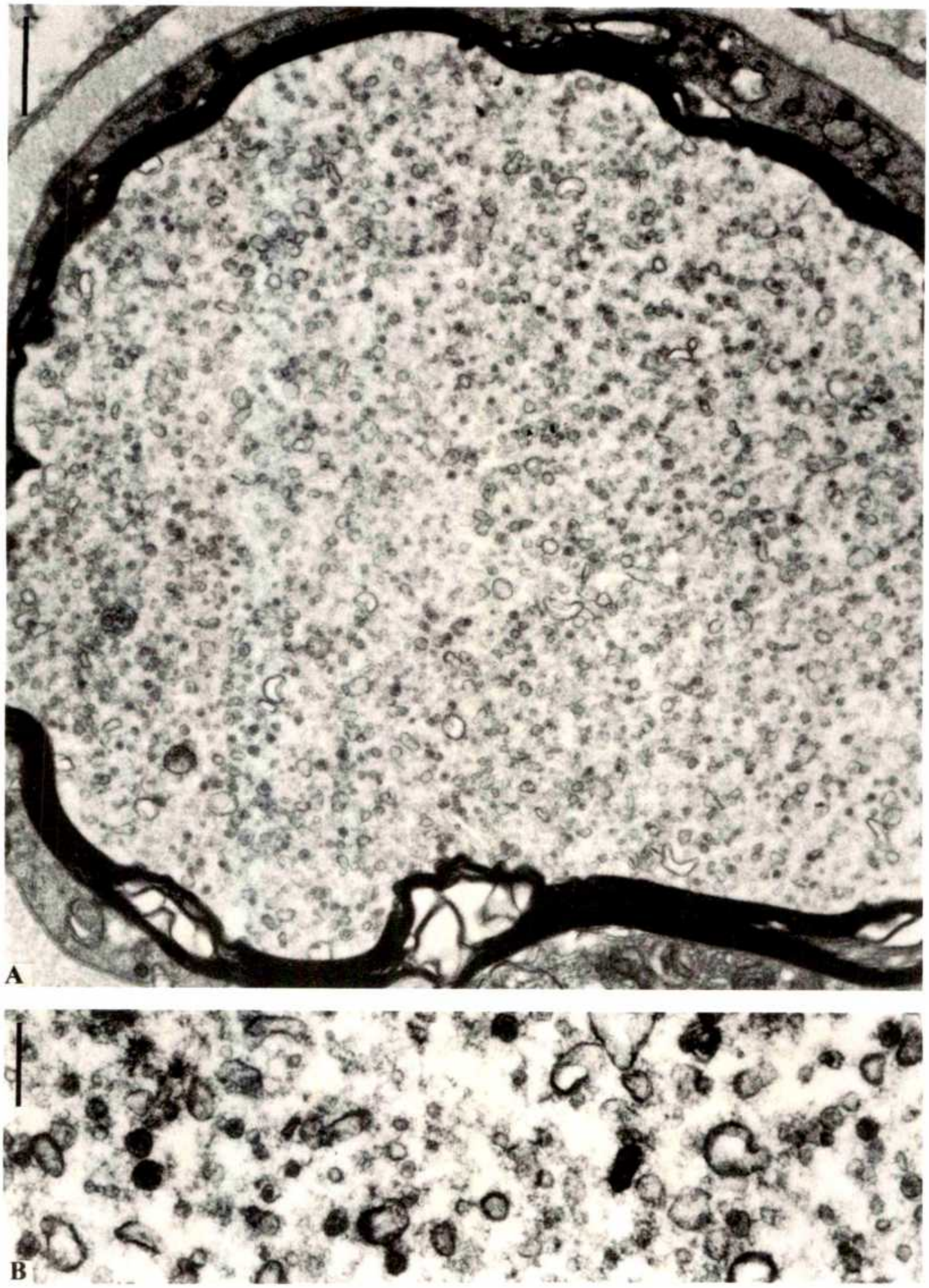

FIG. 5A, myelinated axon distended by vesiculo-tubular organelles with secondary thinning of the myelin sheath. Electron micrograph of transverse thin section of rat sciatic nerve five days after cold injury. Bar = 1.0 μm. B, enlargement of vesiculo-tubular profiles seen in fig. 5A. Bar = 0.3 μm.

Density of Myelinated Fibres

Rat nerves examined 24 h and three days after cooling showed no significant difference in whole nerve myelinated fibre densities, although densities per mm^2 of fascicular area were reduced in both instances because of œdema (Table 2). The density of large, but not small, myelinated fibres per whole nerve did, however, show a decrease in the three day cold group. After five and seven days, cold-injured nerves demonstrated a significant reduction in density of myelinated fibres per whole nerve (Table 2). The decrease in density of both large and small myelinated nerve fibres was highly significant five days after cold injury. However the ratio of large to small myelinated fibre densities in the seven day cold group (2.3 ± 0.6) compared with controls (3.1 ± 0.5) ($P < 0.02$) suggested a more severe involvement of large myelinated fibres. The presence of regenerating fibres two to four weeks after cooling resulted in an increased whole nerve density of small myelinated fibres.

Diameter of Myelinated Fibres

Immediately following nerve cooling the mean diameter of small and large myelinated fibres increased significantly (Table 3) and the distribution of myelinated fibre diameters shifted to the right ($P < 0.001$), (fig. 12). At 24 h, three and five days, mean myelinated fibre diameter of cold injured nerve was reduced. At seven days,

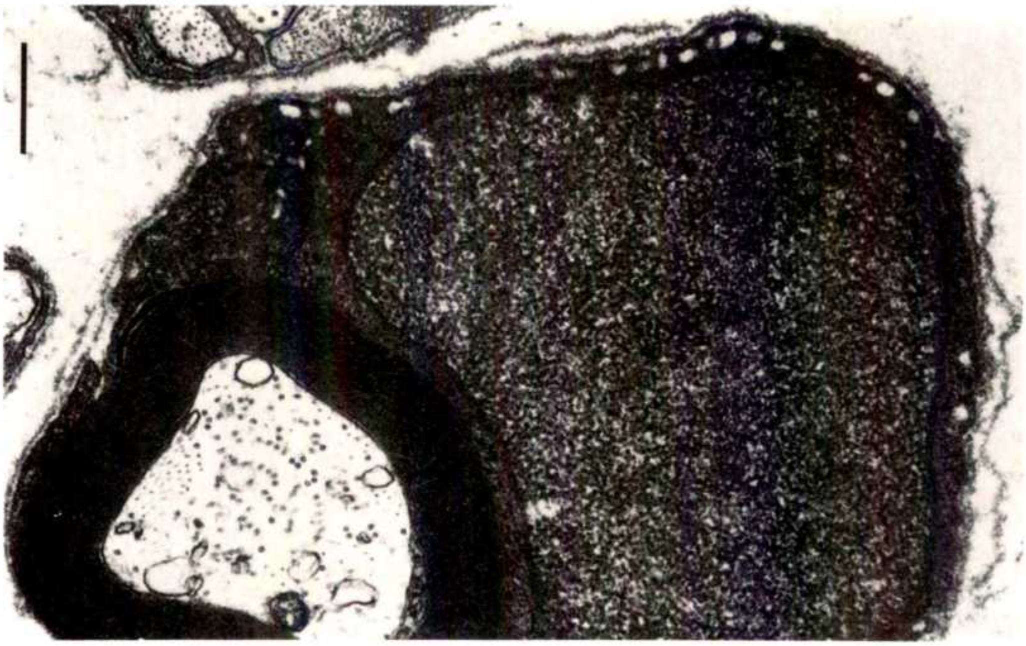

FIG. 6. Schwann cell containing prominent perinuclear vesicles. Electron micrograph of transverse section of rat sciatic nerve twenty-four hours after cold injury. Bar = 0.5 μm.

TABLE 2. MEAN DENSITY OF MYELINATED FIBRES IN SCIATIC NERVES OF COLD EXPOSED RATS AND CONTROLS

Interval after cold	No.	*No./whole nerve* Total	Small[1]	Large[2]	*No./mm²* Total
Control	10	9366 ± 522	2351 ± 386	7015 ± 415	15 918 ± 1021
0 hours	4	9397 ± 685[3]	2135 ± 505[3]	7262 ± 393[3]	14 480 ± 1389
24 hours	5	8814 ± 661[3]	2096 ± 215[3]	6718 ± 672[3]	12 036 ± 991
3 days	4	8615 ± 676[4]	2253 ± 381[3]	6363 ± 487[4]	11 247 ± 825
5 days	4	6065 ± 842[6]	1678 ± 280[5]	4387 ± 598[6]	7626 ± 1060
7 days	10	5467 ± 563[6]	1663 ± 367[6]	3804 ± 590[6]	6326 ± 730
2 weeks	3	8532 ± 325[4]	5012 ± 419[6]	3520 ± 582[6]	10 193 ± 106
4 weeks	3	10 799 ± 1099[5]	5564 ± 965[6]	5235 ± 166[6]	13 976 ± 1607

[1] ≤ 4.46 μm. [2] > 4.46 μm. [3] Not significant. [4] $P < 0.05$. [5] $P < 0.01$. [6] $P < 0.001$.

the two myelinated-fibre populations differed in response, with the small fibre mean diameters increased and that of the large fibres decreased (Table 3). Two to four weeks after cold injury, diameter histograms of myelinated nerve fibres showed a significant increase in the small fibre spectrum (fig. 12).

Unmyelinated Fibres

There was no significant difference in the density of unmyelinated fibres in whole sciatic nerve following cold injury (Table 4). Immediately after cooling the mean unmyelinated nerve fibre diameter increased significantly (Table 3) and the peak of the unmyelinated fibre diameter spectrum shifted to the right ($P < 0.001$) (fig. 13). The mean unmyelinated nerve fibre diameter remained significantly increased up to seven days after cold injury.

TABLE 3. MEAN NERVE FIBRE DIAMETER (μM) OF MYELINATED AND UNMYELINATED FIBRES IN SCIATIC NERVES OF COLD EXPOSED RATS AND CONTROLS

Interval after cold	*Myelinated fibres* No.[1]	Total	Small[2]	Large[3]	*Unmyelinated fibres* No.[1]	Total
Control	22 183	6.57 ± 1.58	3.14 ± 0.86	7.73 ± 1.31	5316	0.72 ± 0.46
0 hours	8154	6.87 ± 1.62[6]	3.21 ± 0.85[6]	7.94 ± 1.38[6]	1916	0.75 ± 0.46[6]
24 hours	11 216	6.49 ± 1.55[5]	3.09 ± 0.87[5]	7.55 ± 1.28[6]	2119	0.74 ± 0.45[6]
3 days	8952	6.41 ± 1.58[6]	3.15 ± 0.87	7.56 ± 1.33[6]	1584	0.75 ± 0.45[6]
5 days	5976	6.50 ± 1.65	3.11 ± 0.87	7.79 ± 1.41[4]	1519	0.76 ± 0.48[6]
7 days	11 754	6.18 ± 1.58[6]	3.23 ± 0.84[6]	7.49 ± 1.34[6]	1956	0.76 ± 0.48[6]
2 weeks	6144	4.73 ± 1.60[6]	2.94 ± 0.88[6]	7.29 ± 1.40[6]		
4 weeks	6397	5.02 ± 1.57[6]	3.04 ± 0.89[6]	7.12 ± 1.35[6]		

[1] Number of fibres measured. [2] ≤ 4.46 μm. [3] > 4.46 μm. [4] $P < 0.05$. [5] $P < 0.01$. [6] $P < 0.001$.

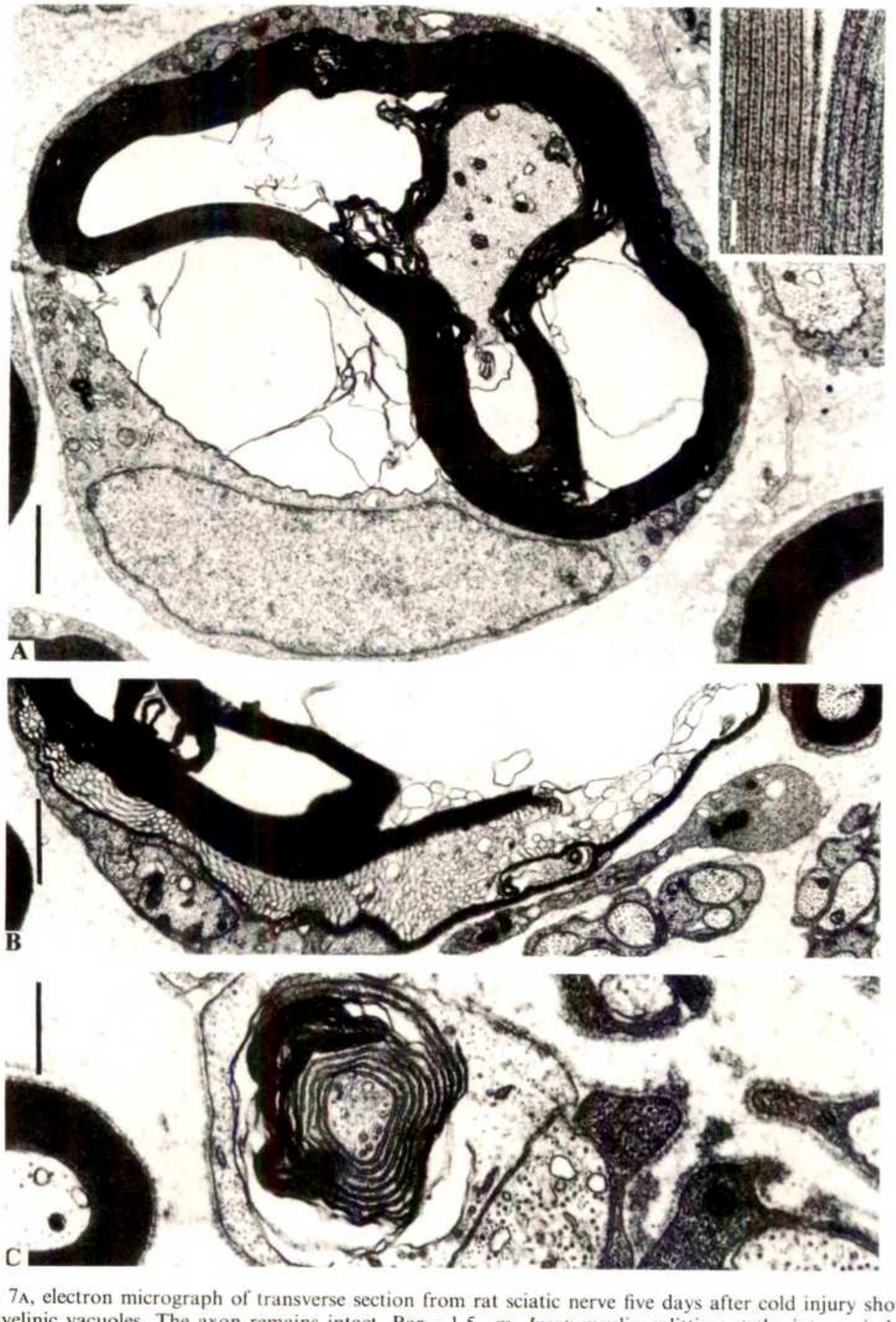

FIG. 7A, electron micrograph of transverse section from rat sciatic nerve five days after cold injury showing intramyelinic vacuoles. The axon remains intact. Bar = 1.5 μm. *Inset*: myelin splitting at the intraperiod line. Bar = 0.05 μm. B, C, two examples of myelin splitting and reordering seen in electron micrographs of rat sciatic nerve seven days after cold injury. B, separation and fusion of myelin lamellæ to form a fine reticulated pattern. Bar = 1.5 μm. C, widening of lamellar spaces. Degenerating wavy lamellar elements have taken on a thicker appearance in the peripheral region of the sheath. Bar = 0.5 μm.

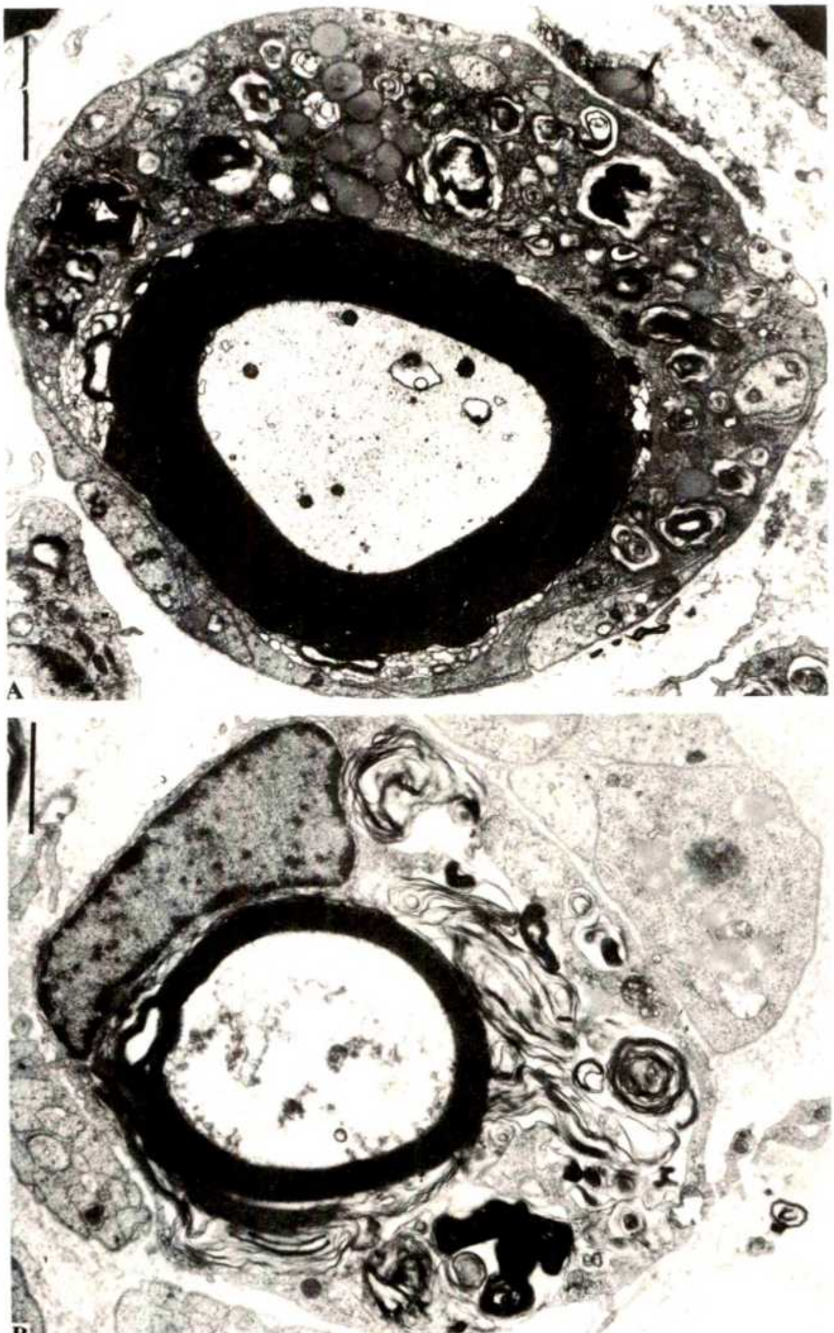

FIG. 8A, electron micrograph of transverse section of rat sciatic nerve five days after cold injury. A macrophage has entered the basal lamina of a myelinated fibre pushing the Schwann cell cytoplasm to the periphery. Note the 'blebbing' of exposed lamellar elements. B, severe axonal degeneration with preservation of myelin lamellæ seen in an electron micrograph of rat sciatic nerve seven days after cold injury. Bars = 2.0 μm.

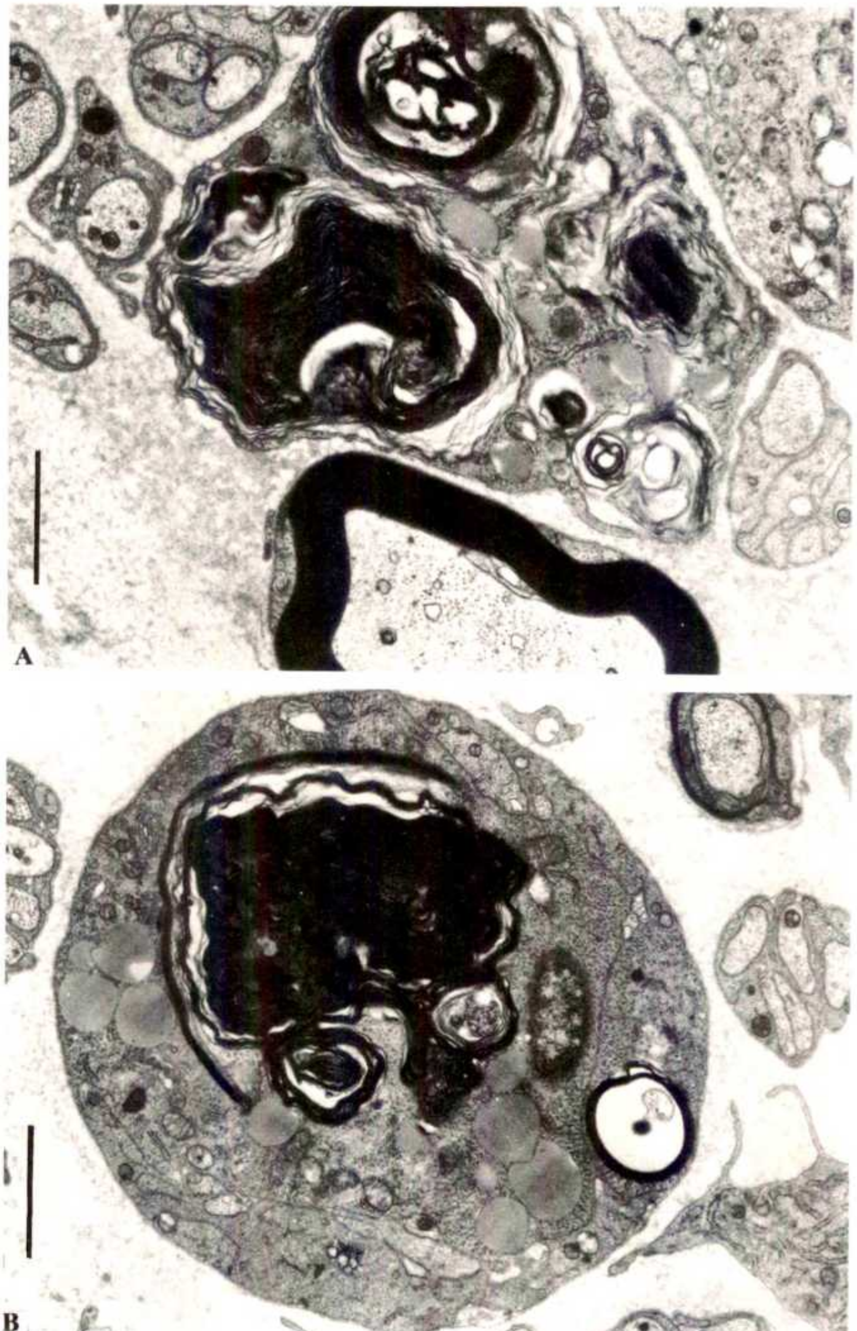

FIG. 9. Electron micrographs from a transverse section through rat sciatic nerve seven days after cold injury showing advanced axonal degeneration. A, a macrophase filled with myelin debris lies juxtaposed to normal myelinated and unmyelinated fibres. B, a Schwann cell contains groups of regenerating fibres, myelin figures and lipid bodies. Bars = 2.0 μm.

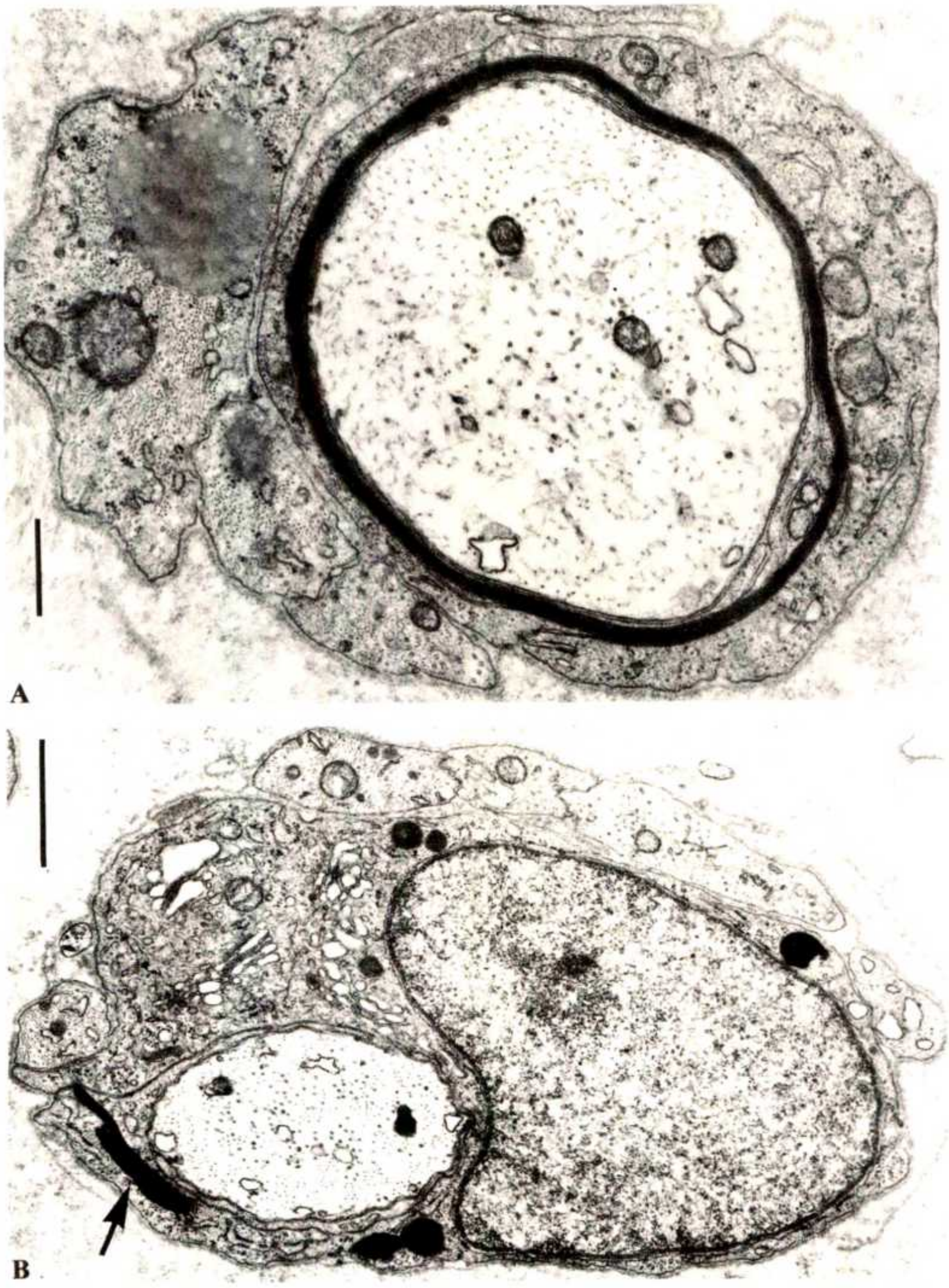

FIG. 10. Electron micrographs of transverse section through rat sciatic nerve seven days after cold injury. A, a thinly myelinated fibre showing either partial demyelination or early remyelination. Bar = 0.5 μm. B, a demyelinated axon. Note Reich granules in Schwann cell cytoplasm (arrow) with dense amorphous components. Bar = 1.0 μm.

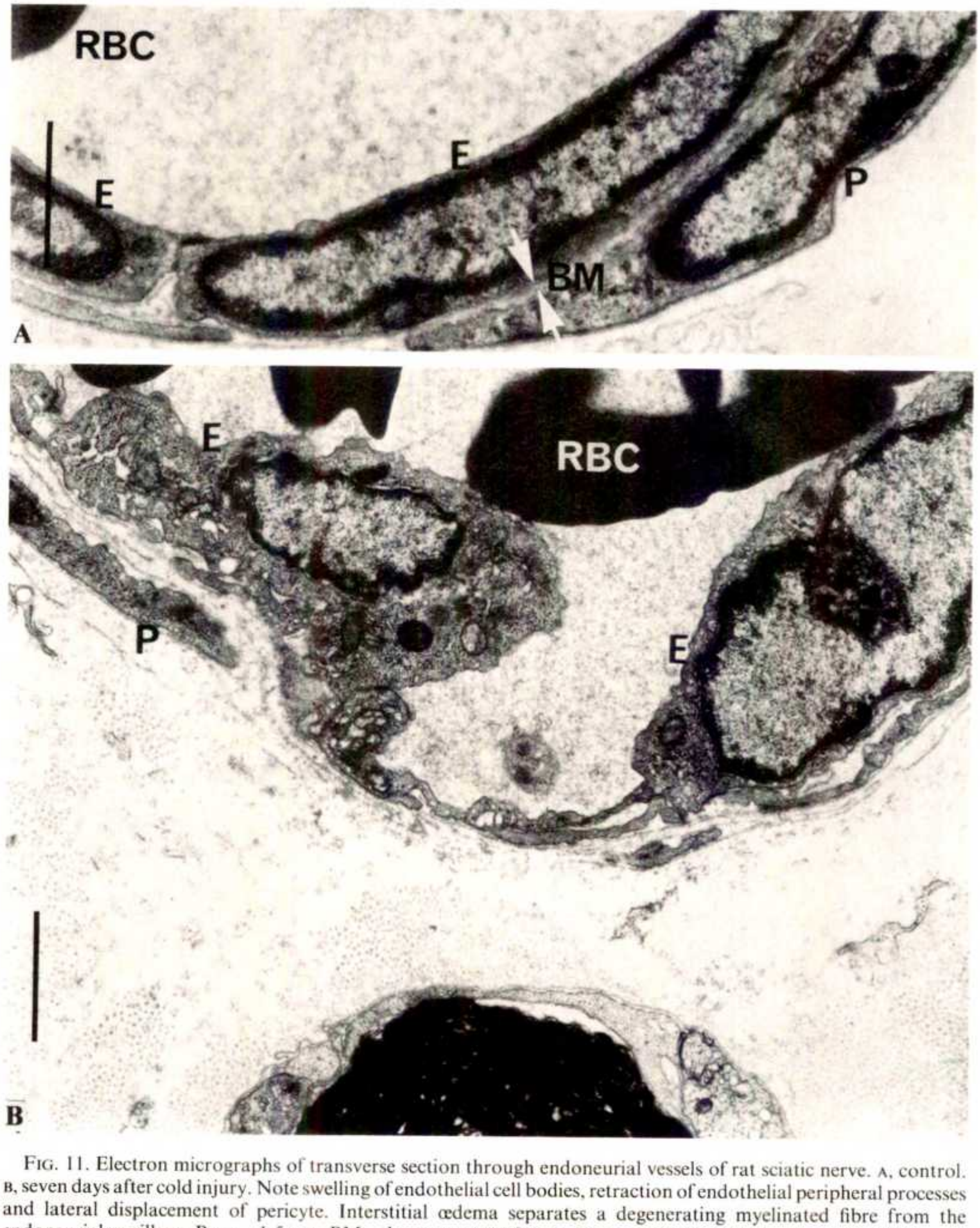

FIG. 11. Electron micrographs of transverse section through endoneurial vessels of rat sciatic nerve. A, control. B, seven days after cold injury. Note swelling of endothelial cell bodies, retraction of endothelial peripheral processes and lateral displacement of pericyte. Interstitial œdema separates a degenerating myelinated fibre from the endoneurial capillary. Bars = 1.5 μm. BM = basement membrane. E = endothelial cell. P = pericyte. RBC = red blood cell.

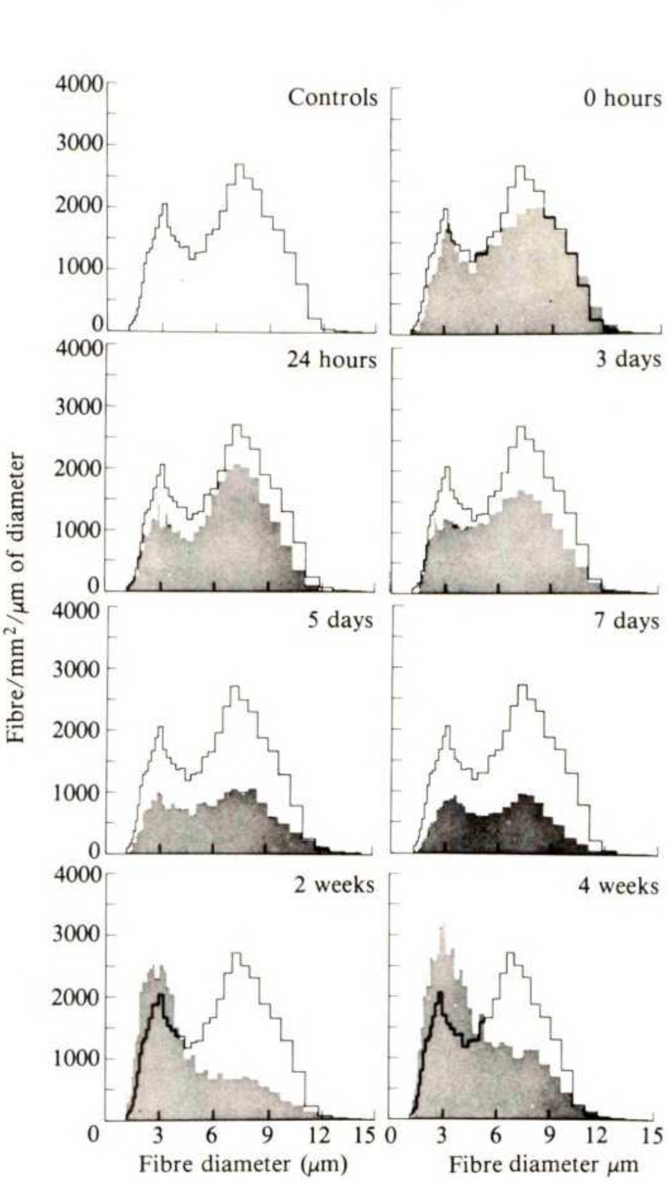

FIG. 12. Diameter histograms of myelinated sciatic nerve fibres from control (non-hatched) and cold-injured nerves (hatched) at intervals of 0 hours, 24 hours, 3 days, 5 days, 7 days, 2 weeks and 4 weeks.

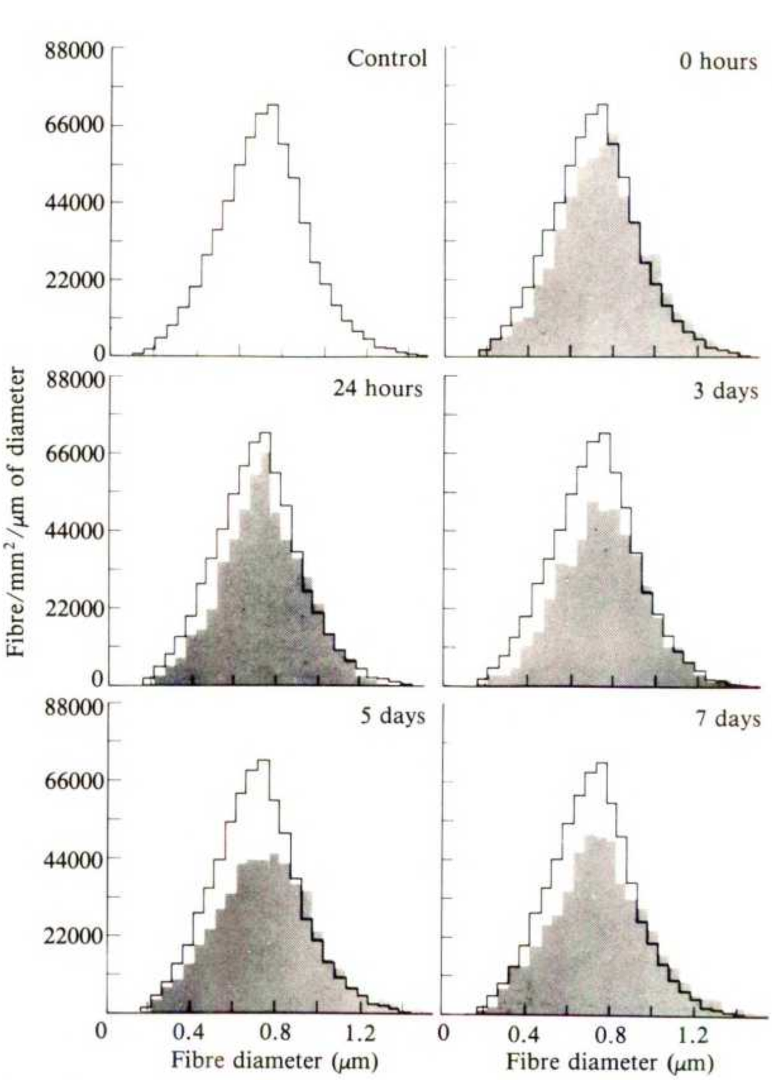

FIG. 13. Diameter histograms of unmyelinated sciatic nerve fibres from control (non-hatched) and cold-injured nerves (hatched) at intervals of 0 hours, 24 hours, 3 days, 5 days and 7 days. The apparent reduction in unmyelinated fibre density results from the plotting of histograms per mm² rather than per whole nerve.

TABLE 4. MEAN DENSITY OF UNMYELINATED FIBRES IN SCIATIC NERVES OF COLD EXPOSED RATS AND CONTROLS

Interval after cold	*No.*	*No./whole nerve*	*No./mm^2*
Control	10	19 925 ± 904	33 892 ± 2368
0 hours	4	20 244 ± 2399	30 603 ± 1980
24 hours	5	20 402 ± 2569	27 783 ± 2808
3 days	4	19 800 ± 2812	25 494 ± 2832
5 days	4	20 813 ± 3146	26 122 ± 3422
7 days	5	22 488 ± 2699	25 539 ± 2178

Quantitative Electron Microscopy

The densities of Schwann cell and macrophage nuclei were significantly increased in the five and seven day cold groups (Table 5), but no significant differences were seen in the number of fibroblast nuclei, denervated Schwann cells or collagen pockets.

Teased Fibre Analysis

Examination of single teased nerve fibres at seven days after cold injury revealed a striking predominance of axonal degeneration (Type E) (Table 6, fig. 14A). At seven days less than 10 per cent of teased nerve fibres showed segmental demyelination. An additional finding was of 16 per cent Type I fibres in which distal internodes exhibited axonal degeneration while proximal internodes were normal or demyelinated (fig. 14B).

TABLE 5. MEAN QUANTITATIVE VALUES OF SCIATIC NERVES IN COLD EXPOSED RATS AND CONTROLS (PER MM^2)

Interval after cold	*No.*	*Nuclei*			*Collagen pockets*	*Denervated Schwann cells*
		Schwann	*Fibroblast*	*Macrophage*		
Control	10	1023 ± 135	387 ± 135	12 ± 25	41 ± 55	0
0 hours	4	948 ± 382	313 ± 135	29 ± 34	30 ± 34	0
24 hours	5	757 ± 234	379 ± 118	24 ± 33	48 ± 65	0
3 days	4	1105 ± 309	470 ± 85	29 ± 34	207 ± 81	0
5 days	4	1855 ± 175[1]	466 ± 186	180 ± 109[1]	215 ± 93	0
7 days	5	2555 ± 866[1]	620 ± 381	244 ± 115[1]	183 ± 114	12 ± 27

[1] $P < 0.001$.

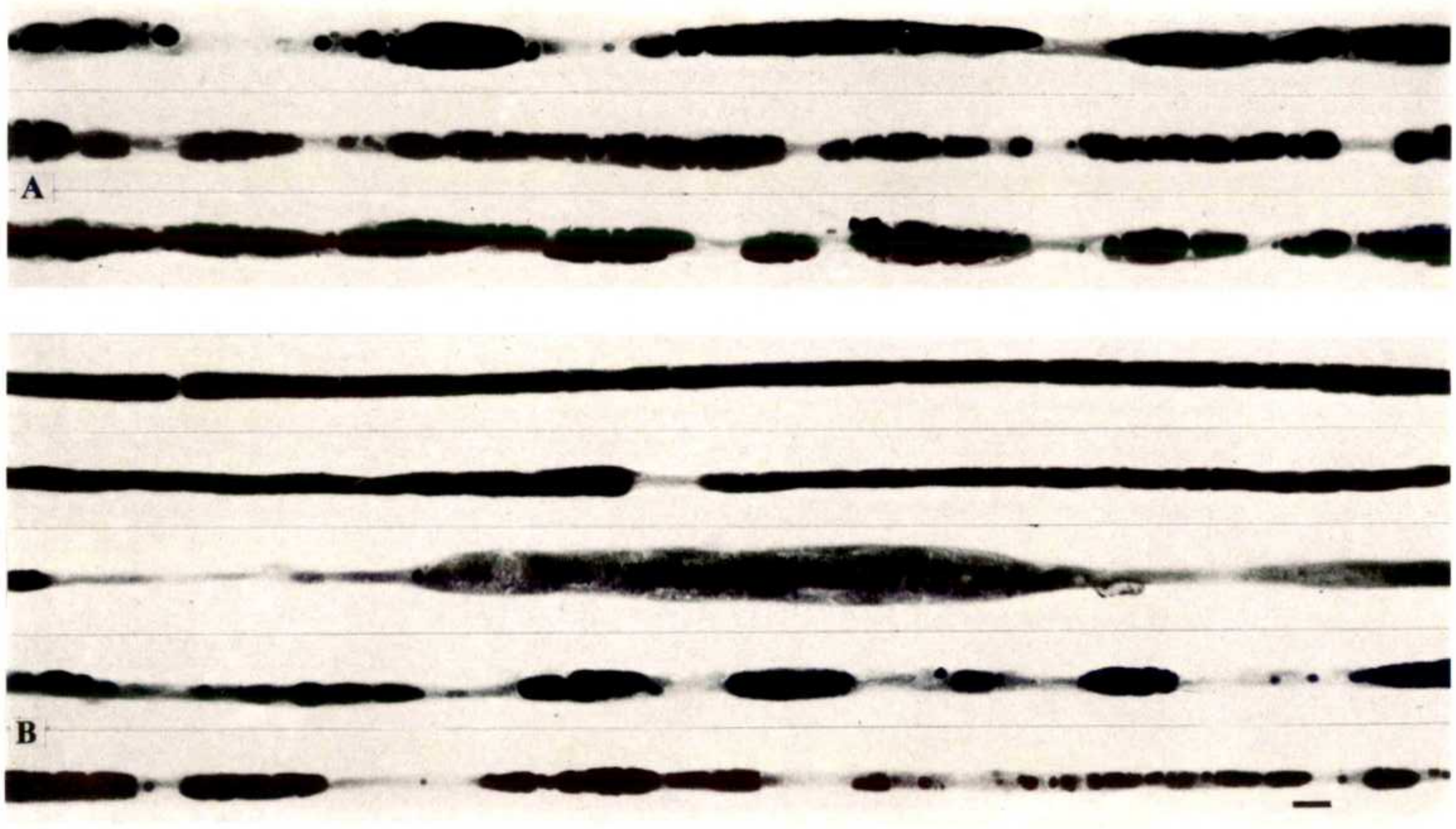

FIG. 14. Consecutive portions of teased myelinated fibres from rat sciatic nerve seven days after cold injury. A, axonal degeneration with linear rows of ovoids (Type E). B, a Type I teased nerve fibre showing proximally a normal internode and adjacent paranodal demyelination and distal swelling and degeneration. Bar = 20 μm.

TABLE 6. GRADING[1] OF TEASED MYELINATED FIBRES IN SCIATIC NERVES OF COLD EXPOSED RATS AND CONTROLS

Interval after cold	*No.*	*Distribution of types of fibres (%)* *A*	*C*	*D*	*E*	*F*	*I*
Control	5	99.5 ± 0.8	0	0	0.2 ± 0.5	0.3 ± 0.7	0
7 days	7	25.9 ± 4.6^{2}	5.0 ± 2.6	0.2 ± 0.4	52.8 ± 7.1^{2}	0.1 ± 0.3	16.0 ± 2.1

[1] A, normal appearance. C, segmental demyelination. D, segmental demyelination and remyelination as evidenced by at least a 50 per cent reduction in myelin thickness. E, linear rows of myelin ovoids and balls. F, segmental remyelination. I, fibre having several proximal internodes or parts of internodes with or without paranodal or segmental demyelination and, distal to those, a linear row of myelin ovoids or balls. [2] $P < 0.001$.

The mean internodal length of normal teased nerve fibres (Type A) was significantly shorter in the seven day cold group than in controls. Likewise the mean internodal length of all normal internodes from seven day cooled nerves was also significantly reduced (Table 7). Demyelinated internodes were randomly distributed in the seven day cold group.

Regression Analysis

The mean regression line of axonal area on number of myelin lamellæ in the seven day cold group was significantly separated from that of controls ($P < 0.01$) (fig. 15) although slopes did not differ.

HRP Studies

In control rat nerve HRP was diffusely present in the epineurium and between outer layers of the perineurium but not within the endoneurial extracellular space. While electron-dense HRP reaction product was observed in multiple pinocytotic vesicles in capillary endothelial (fig. 16A) and inner perineurial cells immediately after nerve cooling it was not seen at this time in the endoneurial extracellular space. In nerve taken 24 h after cooling HRP was also localized around endoneurial capillaries and beneath the perineurium. At three to five days after nerve cooling,

TABLE 7. INTERNODAL LENGTH OF NORMAL TEASED FIBRES AND OF ALL NORMAL INTERNODES IN SCIATIC NERVES OF COLD EXPOSED RATS AND CONTROLS

Interval after cold	*Normal teased fibres* *No.*	*Mean IL*[1] (μm)	*SD*	*Mean CV*[2] (%)	*Normal internodes* *No.*	*Mean IL* (μm)	*SD*
Control	513	1214	206	7.3	2605	1194	236
7 days	141	986[3]	174	7.8	847	986[3]	192

[1] Internodal length. [2] Coefficient of variation. [3] $P < 0.001$.

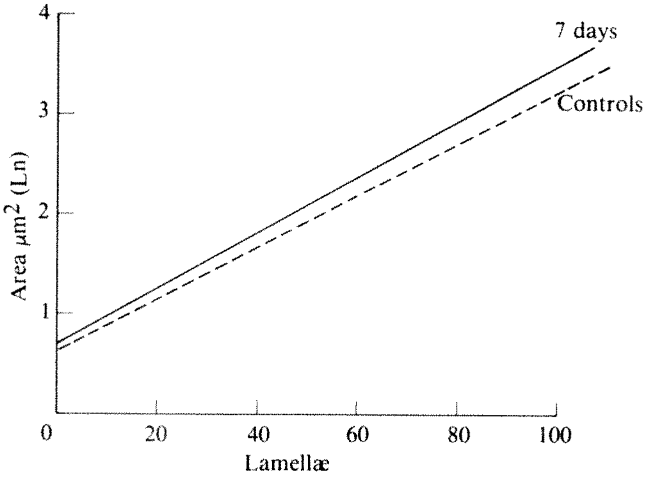

FIG. 15. Mean regression lines for area of axis cylinder (log to base e) and number of myelin lamellæ of rat sciatic nerves in the seven day cold-injured group (solid line, n = 5) and controls (broken line, n = 5).

HRP reaction product was localized in interendothelial clefts (fig. 16B and C) and more diffusely dispersed within the endoneurium. Intramyelinic vacuoles were never stained with HRP reaction produce.

Axonal Transport

Radioactive labelled material accumulated at the proximal end of sciatic nerve segments cooled to 5 or 10° C (fig. 17).

DISCUSSION

Four principal pathological findings require explanation in this investigation of hypothermic lesions in peripheral nerve. An immediate increase in mean diameters of myelinated and unmyelinated fibres, infrequent paranodal and segmental demyelination, marked œdema and a delayed and selective axonal degeneration often associated with organelle accumulation.

The swelling of myelinated axons immediately following cold injury was always followed by axonal atrophy and often by frank axonal degeneration. Axons of Remak cells by contrast remained significantly increased in mean diameter up to seven days after cold injury. It is likely that metabolically-driven mechanisms which normally maintain an optimal exchange of materials and fluid between the axon and endoneurium are suppressed or inactivated by low temperatures and principally responsible for the primary axonal swelling (Blair, 1964). The immediate increase in diameter of myelinated and unmyelinated nerve fibres suggested axonal œdema although this was not confirmed by determining organelle densities. It is of interest that fish acclimatized to 5° C rather than 25° C show a similar increase in axonal

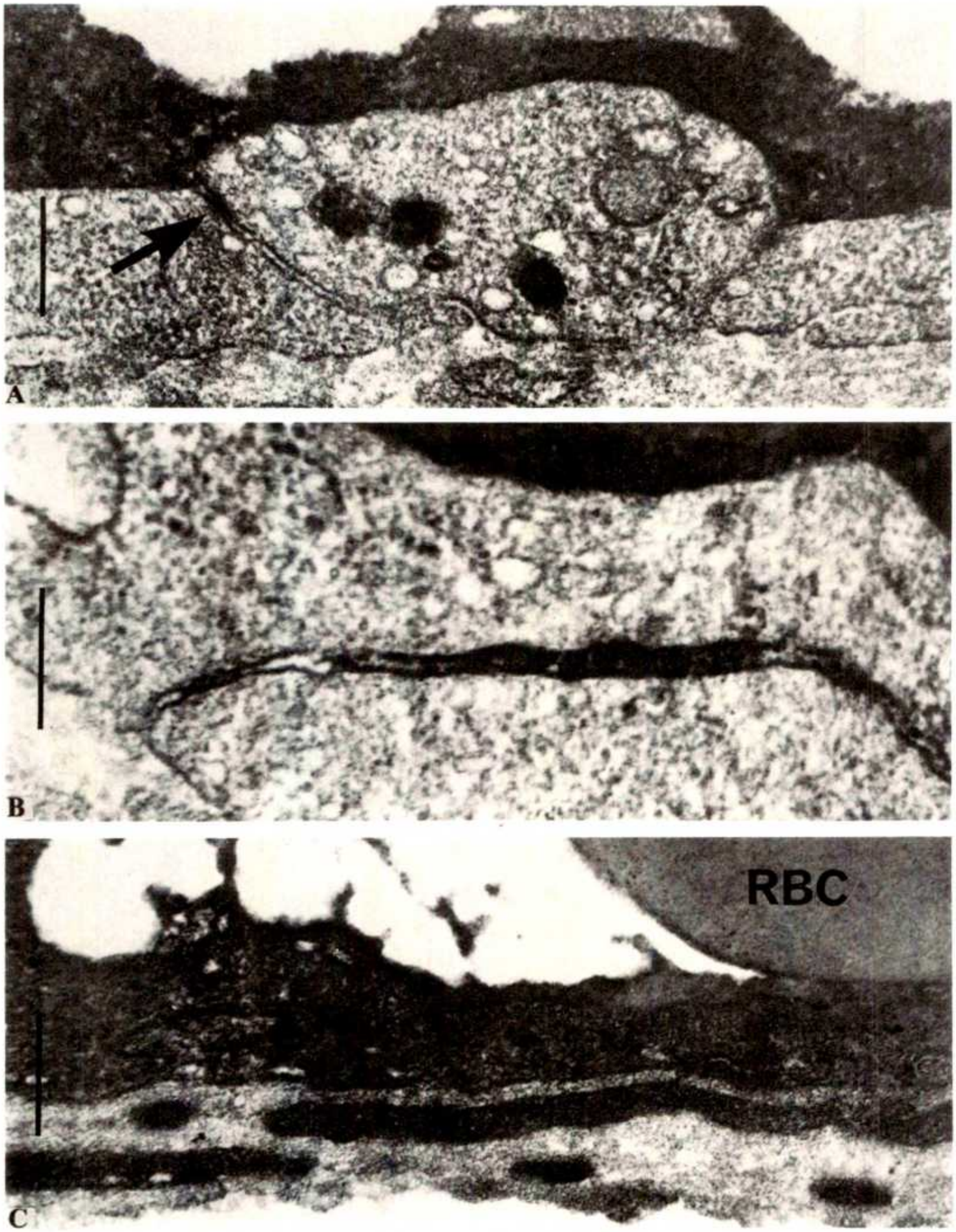

FIG. 16. Electron micrographs of endoneurial vessels from cold-injured rat sciatic nerves. A, HRP reaction product is seen in pinocytotic vesicles within an endothelial cell immediately after cold injury. Only the innermost compartment of the interendothelial cleft, adjacent to the lumen, contains HRP (arrow). B, a long segment of an interendothelial cleft is labelled by high density HRP product, three days after cold injury. C, an endothelial cleft is filled with HRP reaction product five days after cold injury. HRP reaction produce is present in the endoneurial extracellular space. Bars = 0.3 μm. RBC = red blood cell.

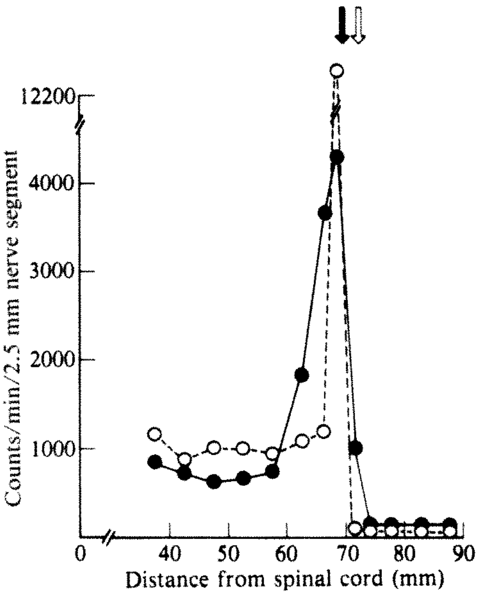

FIG. 17. Block of fast axoplasmic transport by cold. A typical example is shown (filled circles) in which cold (5° C) was applied for two hours to the rat sciatic nerve (filled arrow: proximal end of cooled nerve segment). The contralateral sciatic nerve (open circles) was ligated just prior to cooling contralateral nerve (open arrow: point of ligation).

diameters (Matheson, Diocee and Roots, 1980). Blockade of axoplasmic transport may also have contributed to axonal distention both during the period of cold injury and subsequently when degenerating myelinated fibres were filled with vesiculotubular or membranous structures (Griffin, Price, Engel and Drachman, 1977; Clark, Griffin and Price, 1980). Radioactive tracer experiments have suggested that vesiculotubular structures accumulate with interruption of anterograde axonal transport while large membranous bodies accumulate with a block of retrograde flow (Tsukita and Ishikawa, 1980). Proximal paranodal and segmental demyelination in cold lesions may have been a consequence of axonal swelling with retraction of the myelin sheath (Shimono, Izumi and Kuroiwa, 1978; Spencer and Schaumburg, 1979; Clark *et al.*, 1980). In keeping with the present findings, segmental demyelination has occasionally been encountered proximal to a Wallerian-like degeneration of nerve fibres in experimental acrylamide neuropathy (Sumner, Karreman and Said, 1978).

Increased permeability of endoneurial vessels was an early pathological event in hypothermic nerve injury. Ultrastructural examination showed three routes of funicular barrier permeability to HRP. Twenty-four hours after cold injury HRP was transported by enhanced pinocytosis through perineurial and endothelial cells. Three to five days after cold injury HRP was also visualized in junctional pools indicating a focal opening of endothelial tight junctions. Thus this study shows that blood nerve permeability to HRP, following cold exposure, occurs through two mechanisms: an early energy requiring transportation by pinocytotic vesicles and a late passive interendothelial leakage through damaged endoneurial capillary walls. The delay in hypothermically-induced vasogenic œdema correlates well with the delayed limb swelling seen in trench and immersion foot syndromes (Smith *et al.*, 1915*b*; Ungley *et al.*, 1945).

The progressive increase in endoneurial œdema after cold injury may relate to the absence of endoneurial lymphatics (Sunderland, 1965) which in turn might explain the particular vulnerability of peripheral nerve to hypothermic injury (Blackwood, 1944*a*). Intrafascicular œdema also provides an explanation for the progressive enlargement of whole nerve seen in this cold study. Abnormal vascular permeability of endoneurial vessels, as a delayed phenomenon, has been investigated in various experimental neuropathies (Olsson, 1975; Dyck, Windebank, Low and Baumann, 1980), but the mechanisms remain unclear. Olsson (1968) has suggested it may occur by release of biogenic amines (histamine or serotonin) from mast cells. Of relevance is the recent evidence of a histamine-mediated delayed œdema after thermal injury (Boykin, Eriksson, Sholley and Pittman, 1980).

While œdema within nerve may be strikingly compartmentalized to the interstitium, axon, myelin sheath or the Schwann cell soma, in the present study it had a diffuse distribution. Light microscopy confirmed the presence of interstitial œdema characterized by wide separation of myelinated fibres and the pericapillary and subperineurial accumulation of fluid. The excessive number of vesicles in cooled Schwann cell cytoplasm probably reflected a pre-œdematous state. Intramyelinic œdema was recognized by a characteristic splitting of myelin lamellæ along the intraperiod line or by abnormally widened lamellar spacing. It is noteworthy that when myelin in isolated nerve preparations is exposed to hypotonic solutions, hydration increases in the region of the intraperiod line forcing myelin lamellæ apart (Robertson, 1958; Finean and Burge, 1963). Although the origin of intramyelinic fluid is not known it has been suggested that since nodes of Ranvier are in direct contact with the extracellular space, a main pathway of œdema probably exists from the nodal region (Graham, de Jesus, Pleasure and Gonatas, 1976).

A similar œdematous splitting of myelin lamellæ has been described in peripheral nerve fibres after systemic intoxication with hexachlorophene (Powell, Myers, Zweifach and Lampert, 1978), triethyltin (Graham *et al.*, 1976) or lead (Lampert and Schochet, 1968) and after irradiation (Masurovsky, Bunge and Bunge, 1967). It is pertinent that, despite widespread and severe myelin œdema, axons may be maintained (Masurovsky *et al.*, 1967, Graham *et al.*, 1976).

The present study also demonstrated that following cold injury a slowly progressive peripheral nerve degeneration developed. The reduction of myelinated fibre axon diameter following early axonal enlargement probably represents the early stage of axonal degeneration (Griffin, Price, Hoffman, Clark, Drachman and Pestronk, 1979; Clark *et al.*, 1980). In Wallerian degeneration myelinated and non-myelinated fibres show extensive degeneration 19 to 48 h after injury (Vial, 1958;

Lee, 1963; Thomas, King and Phelps, 1972). These changes were delayed, however, for five to seven days in cold-injured animals. Furthermore, the present findings support the view of a selective vulnerability to cold, based on nerve fibre diameter, with myelination conferring a susceptibility to cold. Thus unmyelinated fibres were not damaged in this investigation while large myelinated nerve fibres were severely affected.

An unexpected finding in seven day cold-injured nerve was of a significantly reduced mean internodal length of normal teased nerve fibres (Type A). Regenerating nerve fibres were neither prominent nor myelinated seven days after cold injury and therefore could not be responsible for the reduction of internodal length. Rather this finding reflects the vulnerability of the largest myelinated fibres to cold injury as evidenced by the reduced ratio of large to small myelinated fibre densities seven days after cold injury.

It is noteworthy with regard to the preferential degeneration of myelinated fibres in cold-injured nerve that cytochemical (Waxman and Quick, 1977; Waxman, 1981), freeze-fracture (Rosenbluth, 1976; Kristol, Sandri and Akert, 1978), and pharmacological studies (Ritchie and Rogart, 1977; Ritchie, 1979) have all shown that the nodal membrane of myelinated fibres is structurally distinct from the membrane of unmyelinated nerve fibres. There are, for example, sparsely distributed sodium channels (35–500/μm^2) in non-myelinated nerve while their density in mammalian nodal membrane is extremely high (10 000/μm^2) (Ritchie, 1979). It is possible that cold might have a direct injurious effect on the nodal membrane and thus preferentially damage myelinated fibres. Moreover, such direct membrane injury might in turn disrupt sodium channels and lead to a conduction block. It is relevant that the cold-blocking temperature of non-myelinated axons is significantly lower than that of myelinated axons (Paintal, 1967; Franz and Iggo, 1968). Moreover, in this study, amplitude of nerve action potentials recovered after cold-induced conduction block to only 56 per cent of normal at a time when axons and myelin retained their ultrastructural integrity.

Alternatively, degeneration of nerve fibres in response to cold injury might be related to endoneurial œdema either because of osmolarity challenge (Sugimura *et al.*, 1980), the release of toxins into the endoneurium or as a result of the likely increase in endoneurial pressure (Powell, Myers, Costello and Lampert, 1979; Myers, Powell, Shapiro, Costello and Lampert, 1980).

Another suggested pathogenic mechanism in cold-induced neuropathy is ischæmia (Smith *et al.*, 1915*a*, *b*; Lake, 1917; Ungley and Blackwood, 1942; Blackwood and Russell, 1943; Large and Heinbecker, 1944; Denny-Brown *et al.*, 1945). However, while there is both clinical and pathological evidence of ischæmia in severe cold lesions (Webster *et al.*, 1942; Blackwood, 1944*b*; Friedman, 1945; Dunning, 1964) there is less clear evidence of vascular pathology in the mild syndromes of cold-induced neuropathy. Indeed in the present model of hypothermic injury the delayed onset of axonal degeneration and the slow progressive course would seem to argue against this possibility. However, the demonstration in vasa nervorum of retraction of endothelial processes and of a breakdown in endothelial tight junctions strongly supports the concept of vasculopathy, even in cold injury morphologically assessed as mild.

In an experimental study of ischæmic neuropathy, Hess, Eames, Darveniza and Gilliatt, (1979) have demonstrated extensive axonal degeneration without selective loss of nerve fibre. However, on teased nerve fibre analysis, some fibres showed normal myelinated internodes proximally and axonal degeneration distally (Type I fibres), similar to the findings in cold lesions. The new elegant model of ischæmic peripheral neuropathy provided by Parry and Brown (1980) has shown involvement of both myelinated and unmyelinated fibres with small myelinated fibres most susceptible to ischæmia. In addition Korthals, Korthals and Wisniewski (1978) noted a focal accumulation of organelles in distal ischæmic axons. On the basis of this finding it was postulated that ischæmia might precipitate nerve degeneration *via* a block of axoplasmic transport. Thus ischæmia of peripheral nerve might lead either directly or indirectly to axonal degeneration.

In the clinical angiopathic neuropathy of rheumatoid arthritis Dyck, Conn and Okazaki (1972) have emphasized a central fascicular pattern of nerve fibre degeneration. At the site of greatest nerve fibre injury both intact myelinated and unmyelinated fibres were absent. Asbury and Johnson (1978) have by contrast stressed the vulnerability of bridging interfascicular bundles in peripheral nerve ischæmia. They emphasized that the vasculitides often resulted in nerve infarction, involving crescent-shaped fascicular areas or entire fascicles. Moreover, zones of ischæmia often extended from endoneurium into the epineurium. Localized infarction with peripheral nerve 'softening' was not demonstrated in this cold study.

Present experimental and clinical evidence therefore suggests that ischæmia is an unlikely cause of the selective and widespread loss of myelinated fibres in cold-injured nerve.

Could myelinated fibre degeneration be related to a cold-induced suspension of axoplasmic transport? It is well-known that fast axoplasmic transport is blocked by cold (Edström and Hanson, 1973; Ochs and Smith, 1975; Brimijoin, Olsen and Rosenson, 1979). A severe reduction in number of microtubules has been demonstrated after cold treatment and reformation of microtubules seen with rewarming (Tilney and Porter, 1967; Rodriguez Echandia and Piezzi, 1968; Rome-Talbot, Andre and Chalazonitis, 1978). The role of axoplasmic transport in the pathogenesis of axonal swelling has also been investigated. Griffin *et al.* (1977), using electromicroscopic autoradiography, found axons swollen with densely-packed membranous organelles after ligation. In addition, rapidly transported labelled proteins were strictly associated with these organelles. In this cold experiment, fast axoplasmic transport was blocked by local hypothermia and axonal swelling, and accumulation of organelles and paranodal demyelination was seen. However, the initial neurophysiological recovery and the reported rapid return of normal axoplasmic flow following cold blockade (Ochs and Smith, 1975) suggested that alteration in the dynamics of fast axoplasmic transport during cold injury did not play an important role in the production of the delayed axonal degeneration.

The clinical presentations and natural history of cold injury syndromes have been clearly defined. Descriptions of trench foot emphasize paralysis, marked anæsthesia and swelling of the lower extremities (Smith *et al.*, 1915*a*, *b*). The present morphological findings would approximate most closely to this syndrome.

The cold immersion foot syndrome typically constitutes a more severe lesion, often with general body cooling and intense reflex vasoconstriction (Lake, 1917; Ungley *et al.*, 1945). The pan-sensory loss is often extensive and associated with autonomic involvement (anhidrosis) in the distribution of analgesia (Webster *et al.*, 1942; Ungley *et al.*, 1945). Gangrene, typically superficial and localized to the digits, is seen in the more severe cases. Histologically both myelinated and unmyelinated fibres are affected (Blackwood, 1944*b*). This syndrome is to be distinguished from warm water and tropical immersion foot syndromes (Allen and Taplin, 1973), arising from the damaging effects of prolonged water immersion on the skin. Although these two tropical syndromes result in painful feet they produce no neurological sequelæ.

In frostbite there is freezing of tissue with necrosis, especially of the superficial soft tissues (Greene, 1941; Bigelow, 1942; Davis, Scarff, Rogers and Dickinson, 1943; Miller and Chasmar, 1980). Once the temperature of nerve drops below freezing for more than a few seconds, nerve degeneration always results, affecting all nerve fibres equally. Indeed, histological sections reveal complete necrosis of all structures within the perineurium except the endothelial lining of blood vessels (Denny-Brown *et al.*, 1945). In some patients, distal frostbite shades off to a milder hypothermic lesion proximally.

This evidence therefore suggests that a continuum exists between the relatively mild hypothermic lesion of trench foot, the intermediate syndrome of immersion foot, and the severe necrotic lesion of frostbite. Moreover, this gradient of clinical severity would appear to be matched in peripheral nerve by an increasingly severe morphological change, progressively involving myelinated fibres, unmyelinated fibres and finally, the entire endoneurium.

SUMMARY

Focal non-freezing injury to rat sciatic nerve resulted in nerve conduction block and cessation of axoplasmic transport. Rats showed early functional recovery but subsequently developed a slowly progressive sciatic nerve paralysis. Horseradish peroxidase studies revealed prominent nerve œdema with early enhanced pinocytosis and later, passive leakage through damaged endoneurial capillaries.

Detailed microscopy indicated a striking selective vulnerability to cold based on nerve fibre diameter. Unmyelinated fibres were spared while large myelinated nerve fibres showed severe axonal degeneration. Paranodal and segmental demyelination were infrequent findings and may have resulted from early axonal swelling. Possible pathogenic mechanisms to explain the degeneration of myelinated fibres in hypothermic injury are discussed.

It is concluded that the gradient of clinical severity seen in limb hypothermic injuries has a pathological correlate in peripheral nerve.

ACKNOWLEDGEMENT

This study was aided by a grant from the Medical Research Council of New Zealand.

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(*Received April 22, 1981*)

Brain (1981), **104**, 813–840

A NEW CLASS OF VISUAL DEFECT

SPREADING INHIBITION ELICITED BY CHROMATIC LIGHT STIMULI

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INTRODUCTION

WE report the results of an investigation on a single male subject, M., who suffers from a visual functional abnormality of a kind not previously reported. The subject has been aware of his abnormal visual responses since childhood and has been studied by the vision research group at Imperial College over the last ten years. A number of shorter papers describing aspects of M.'s vision have been published (Barbur, Ruddock and Waterfield, 1979; Bender and Ruddock, 1974; Ruddock and Waterfield, 1978), but we have recently had the opportunity for a period of intensive study on M., in the course of which we have discovered major new response features. In particular, we have demonstrated that red stimuli release a powerful, spreading inhibition which suppresses his detection of high contrast black and white targets. In this report, we present our new results, together with a selection of data obtained in earlier studies, in order to provide as complete a description as possible of M.'s visual responses. In the Discussion section, we argue that M.'s responses have important implications for the understanding of central visual organization.

PATIENT AND METHODS

Subject M. is a 30-year-old male, who was referred to us by an employer as a consequence of problems associated with his colour vision. Extensive ophthalmic investigation revealed no trace of abnormality in the ocular media or fundus, and his visual acuity in black and white corresponds to 6/4 vision (uncorrected) in either eye. As mentioned in the Introduction, he has been aware of his abnormal vision since childhood, but there is no record of treatment with unusual drugs, no unusual medical history and no recorded accident. The defect has remained entirely stable during the ten years of study at Imperial College. Tests carried out on his family, including a single male offspring, have revealed no other cases of the defect, although there is congenital red-green colour vision deficiency in both maternal and paternal families. In both cases, it is probably a deutan defect, but precise colorimetric examination has not been possible. Thus certain features of M.'s responses may reflect congenital red-green defective colour vision, which is essentially a retinal abnormality. We will show, however, that the principal features of the defect are central in origin and are quite unlike those associated with the standard congenital colour vision deficiencies. Data are also given for a number of subjects with both normal colour vision and normal stereoscopic function and for a single protanope.

Experimental Methods

A variety of different methods have been applied in the characterization of M.'s visual function, and the detailed instrumentation and experimental methods can be found in the cited references. Colour matching and two-colour increment threshold data were both obtained with the tristimulus colorimeter designed and constructed by Wright (1927/28, 1946). Experiments with moving and transient stimuli were performed with a Maxwellian viewing system designed specifically for such studies (Barbur and Ruddock, 1980*a*). The white light source of this instrument, a quartz halogen-tungsten lamp of colour temperature 3400K, was filtered through Balzer B40 interference filters (wavelength bandwidth ±5 nm) to provide near monochromatic stimuli as required. All optical instruments were provided with artificial exit pupils, and the subject's head position was maintained with a dental clamp. Stereoscopic vision was assessed with Julesz (1971) random dot stereograms, in the two-colour anaglyph form, and these were viewed through specially constructed spectacles, consisting of a red (630 nm) and a green (530 nm) interference filter, placed one over each eye. The characteristics of the spreading inhibitory effect were most readily investigated by observations with surface colours printed on cards. These were viewed in normal daylight and their chromaticity co-ordinates were determined either by measurement of their spectral reflectance factors with a Beckman DK2 recording spectrophotometer, from which the co-ordinates were derived by standard computational methods (*see* Wright, 1969), or with a Hilger and Watt J40 Colourmeter.

RESULTS

The Parametric Properties of the Inhibitory Spreading Effect

M. cannot detect small or dim red targets and when they are larger or brighter, he reports that they appear as 'a diffuse grey area, with a metallic, silvery sheen'. Further, high contrast black and white targets, which he can readily resolve when seen in isolation, disappear when either superimposed on, or *located adjacent to* a red surface colour. This is illustrated by fig. 1, in which M. has sketched the appearance of high contrast black on white targets located near red areas. The sketches show that small red stimuli are undetected, but as their size increases, they are seen as a diffuse, silvery-grey area, which spreads around the visual field region occupied by the red stimulus. High contrast targets of both polarities (black on white and white on black) are obscured when located within this grey area, and the effect also occurs under dichoptic presentation of the stimuli, that is, with the inhibitory red stimulus presented to one eye and the high contrast black and white targets to the other. Fig. 1 shows that the field area over which M. perceives a 'silvery-grey' effect depends on the size of the red stimulus and in order to obtain an estimate of the full extent of the effect, we placed on a white background circular black targets, of several sizes, at various distances from an 18 × 14.5 deg oblong red area (chromaticity co-ordinates, $x=0.492$; $y=0.316$, luminance factor $Y=12.6$). The luminance factor of the black targets was 6 and that of their white background 90, giving a large luminance ratio of 0.07. M. detected the 'silvery-grey' effect up to 12 deg from the long edge of the red stimulus, within which area black targets of diameter some ¼ deg were undetected. Targets of diameter ½ deg were undetected for up to some 5 deg from the edge, but at other points within the 'grey' area, appeared as dark, blurred regions of dimension about twice that of the target itself; 2 deg diameter targets appeared blurred up to some 6 deg from the edge, but were then seen sharply. The expression of the inhibitory effect associated with the stimulus therefore depends upon the nature of the target, as well as on the inhibitory stimulus, but we have not investigated this aspect in any detail. The inhibitory effect is observed at all locations in the visual field, and the suppression of high contrast targets by non-overlapping red stimuli occurs both when M. fixates the target region and when he fixates the region of the inhibitory red stimulus. Under monoptic viewing conditions, the grey area extends across the midline of the field; by providing a 2 deg target on which M. could fixate, we found that with the edge orientated parallel to and located some 4 deg from the vertical meridian, the grey inhibitory region spread across the vertical meridian for at least 4 deg into the opposite half-field.

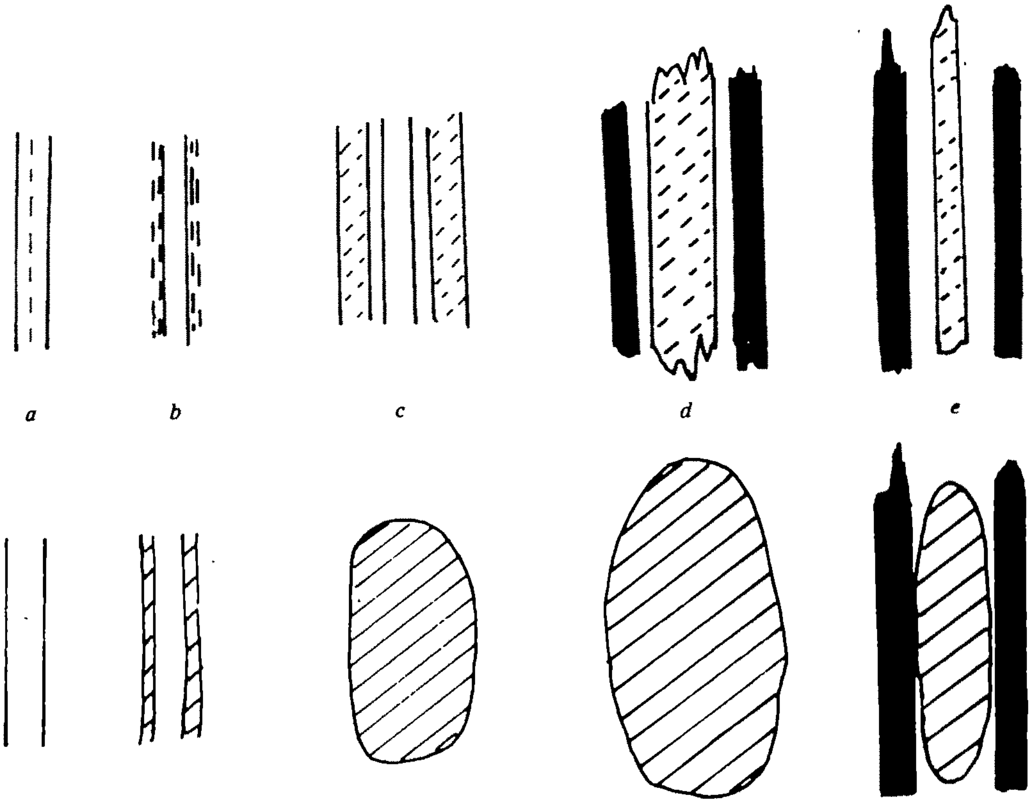

FIG. 1. The upper row shows a set of five stimulus patterns (*a* to *e*), consisting of black bars, denoted by the fully shaded areas and red bars, denoted by the broken lines or hatched areas. The lower row shows M.'s hand-drawn illustrations of the appearance of these patterns; the hatched areas denote regions which appeared 'silvery-grey' and the fully shaded areas appeared black, with well-defined edges.

Two aspects of the inhibition effect could be conveniently studied with surface colours: first, the variation with the size of a red stimulus in the spread of the inhibition and secondly, the dependence of the effect on the colour of the inhibitory stimulus. The method of measurement is illustrated in fig. 2A. Two rows of high contrast black targets, one full and the other open circles, were printed on to a white card, and this card placed against the inhibitory stimulus with the line of the 12 min circular targets, with centre to centre separation of 34 min arranged perpendicular to the stimulus edge. The inhibitory effect was characterized by two measures: the distance from the edge, l_s, at which the targets could just no longer be detected and the distance, l_b, at which they just appeared blurred. For those inhibitory stimuli which gave small effects, measurements with a line of smaller (3.4 min diameter) targets gave more accurate results. The change of the inhibitory area with change in stimulus size is shown in fig. 2B, in which the inhibitory area, A_i (equal to the stimulus area added to the surround area extending to distance l_s or l_b from the stimulus edge) is plotted against the area of the square-shaped inhibitory stimulus, A_s. The value of A_i is linearly related to A_s, implying extensive summation over the area of the inhibitory stimulus. We observed, however, that the inhibition extends further from the short than from the long edge of a red oblong, thus it is not simply area which determines the spread of the effect.

The inhibitory effect was measured for a series of different colour samples (Royal Horticultural Society colour chart), viewed at a fixed distance such that they subtended 5 deg × 3.7 deg at the subject's eye. The results are given in fig. 3A, in which the different symbols on the C.I.E. 2 deg chromaticity chart (Commission Internationale de l'Eclairage, 1931) indicate the distance over which the inhibition extends from the colour samples, zero effect being denoted by a full triangle. The diagram demonstrates that inhibition is associated with the red-purple region of the chromaticity chart and is somewhat greater for saturated than for desaturated colours. No effect was observed with yellow samples, but there is a small effect for a green ($x = 0.266$; $y = 0.515$) and a blue ($x = 0.275$; $y = 0.20$) sample. A more detailed description of the colour dependence illustrated in fig. 3A was obtained by measurement of l_b (i) for samples of approximately the same saturation and chromaticity (that is, constant colour co-ordinates x and y), but of different luminance factors, Y, the variable which correlates with the apparent brightness of the sample, and (ii) as a function of saturation for samples of constant luminance factor (approximately equal to 12), lying on a straight line between the white point, W, and a fixed point (620 nm) on the spectrum locus. The number of available samples with constant chromaticity, but different Y-factor was very restricted, thus the data (fig. 3B) show only the general trend of the relationship between Y and l_b, but for each of the three chromaticity values investigated, l_b increases as Y increases, the relationship between them being clearly dependent on the chromaticity co-ordinates of the samples. Rather more extensive data are given for the variation of l_b with saturation, expressed in terms of the variable Y_s (Equation 5, Appendix). It is apparent that as Y_s and therefore the saturation increases, the value of l_b rises

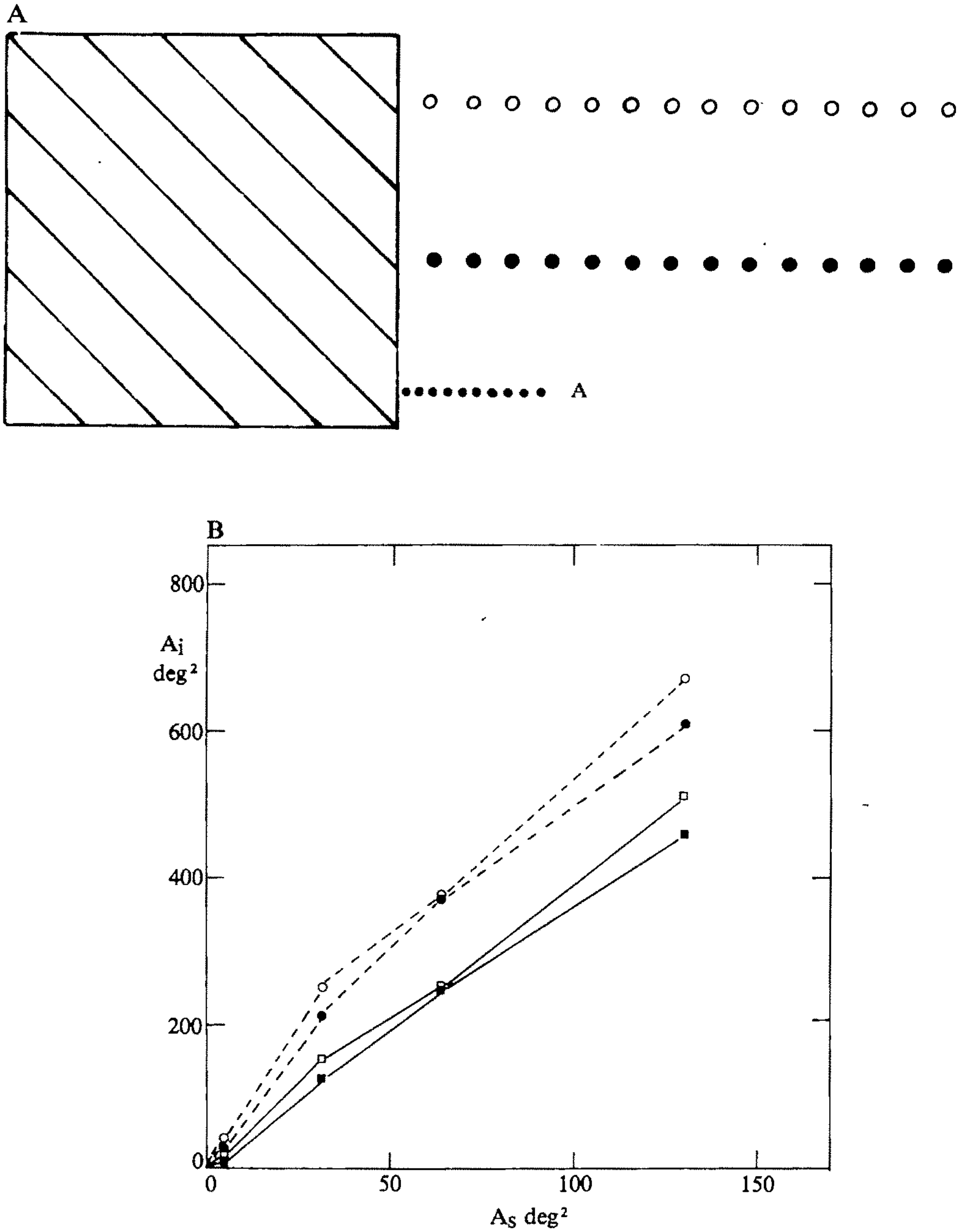

FIG. 2A, illustrating the method used to measure the spread of inhibition around a coloured stimulus, represented by the hatched square. The subject was asked to identify the positions at which the circular targets could just not be detected (distance l_s from the edge of the square) and at which the targets first appeared to have blurred edges (distance l_b from the edge of the square). B, the area, A_i, covered by the inhibitory responses plotted against the area of the square inhibitory stimulus, A_s. Squares correspond to the area of a square with side length $(2l_s + \sqrt{A_s})$ and circles to the area of a square of side $(2l_b + \sqrt{A_s})$. Data were measured for 12 min diameter circular targets of the kind illustrated in A; open symbols for open targets, full symbols for full targets. Subject M.

rapidly after the threshold value, $Y_s \simeq 5.8$, has been exceeded. Thus for constant stimulus luminance, Y, the spread of inhibition increases with stimulus saturation.

A few check measurements were made with four large (23.5 deg × 16.5 deg) colour samples, one red (x = 0.553; y = 0.312; Y = 11.4), one yellow (x = 0.425; y = 0.472; Y = 59), one green (x = 0.274; y = 0.415; Y = 15.8) and one blue (x = 0.167; y = 0.105; Y = 6). The location of these four colours on the chromaticity chart are denoted by R, Y, G and B, respectively (fig. 3A), and the results were consistent with

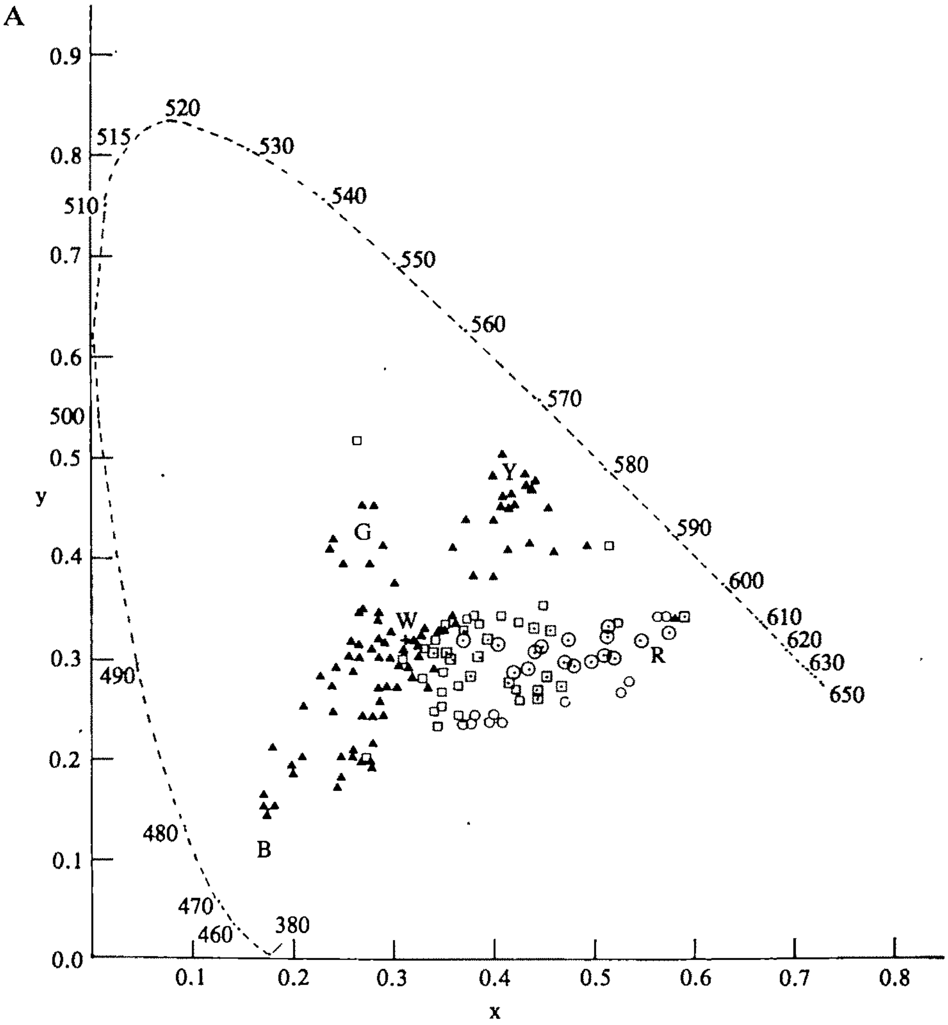

FIG. 3A. C. I. E. 2 deg x-y chromaticity chart showing the value of l_s for 5 × 3.7 deg stimuli with chromaticity co-ordinates denoted by the data points. Values l_s were measured from the short side of the stimulus, for 12 min circular black targets. Different symbols denote different ranges of values of l_s: ⊙ = $l_s > 3$ deg; ⊡ = 1.7 deg $\leqslant l_s \leqslant$ 3.0 deg; ○ = 0.23 deg $\leqslant l_s <$ 1.7 deg; □ = $l_s < 0.23$ deg. Full triangles denote zero effect. W denotes the white point (source C), R, G, B and Y and co-ordinates of four 23.5 × 17 deg stimuli (*see text*), and the numbers denote the wavelength (nm) of spectral stimuli on the spectrum locus. Subject M.

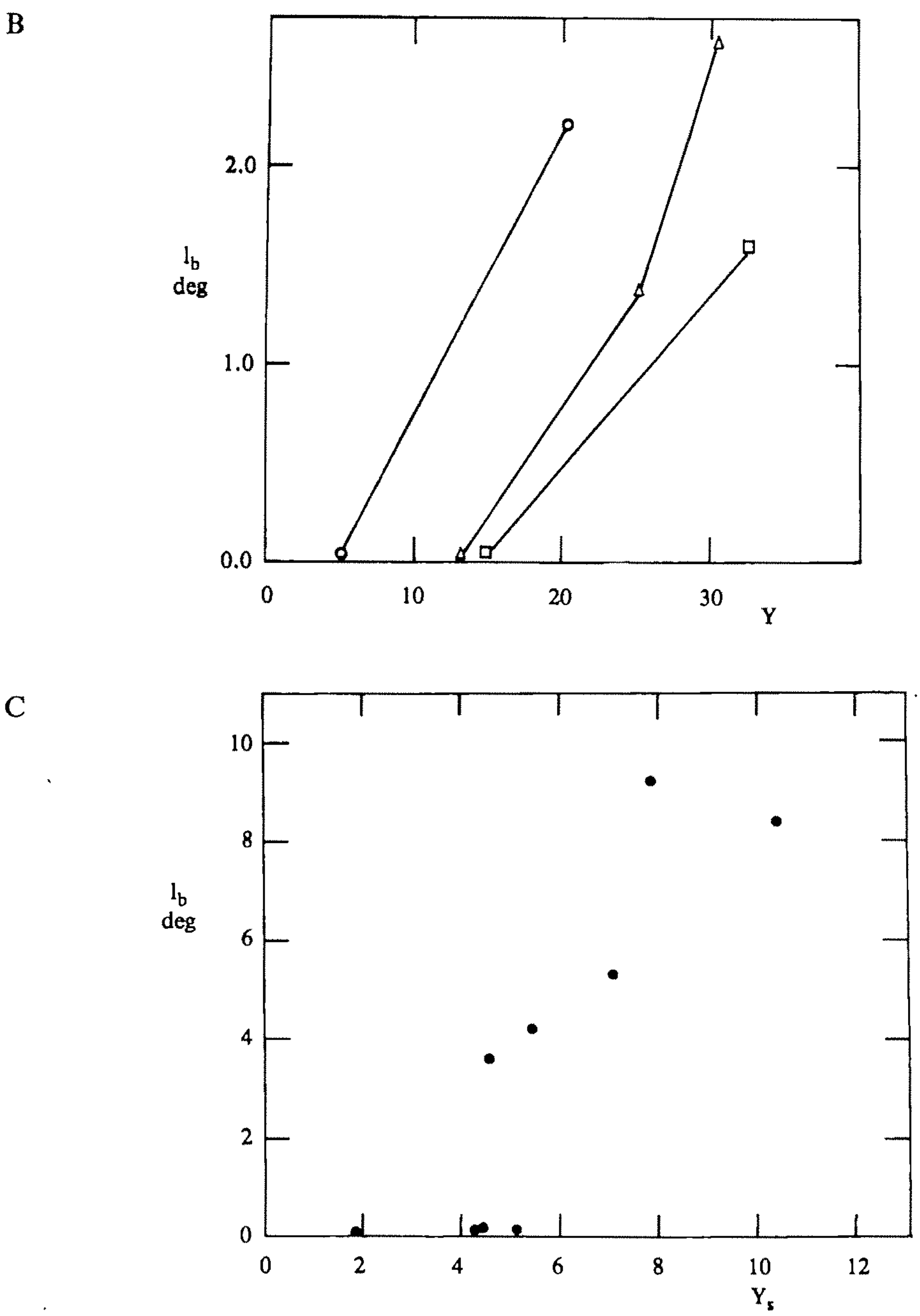

FIG. 3B, values of l_b plotted against the luminance factor, Y, of the stimulus. Each symbol refers to stimuli with different chromaticity co-ordinates; circles (0.475, 0.296), triangles (0.423, 0.286) and squares (0.445, 0.330). Subject M. 3C, values of l_b plotted against the luminance factor Y_s (equation 5, Appendix) of stimuli with constant Y factor, equal to 12, and lying on a line joining the white point, W, to the wavelength 620 nm on the spectrum locus (fig. 3A). Subject M.

those obtained for the smaller samples in showing a very large effect for the red sample, small effects for the green and blue but no effect for the yellow, despite its very high luminance factor.

The observations described in this section demonstrate that M.'s visual defect is essentially inhibitory, is markedly colour dependent, is dichoptically transferred, and generates a signal which spreads over at least 12 deg, crossing the midline by at least 4 deg. In the remainder of the Results section, we present M.'s data for a number of different psychophysical responses.

Visual Threshold Sensitivity

Wavelength dependence. M.'s threshold sensitivity for detection of a foveally fixated, 1 deg circular target of wavelength λ is plotted in fig. 4A, together with comparison data for a normal subject. These data demonstrate large loss of sensitivity in M.'s detection of near-monochromatic targets, being most marked for $\lambda \geqslant 610$ nm, the wavelength range for which the spreading inhibition is greatest. The smallest sensitivity defect occurs with blue stimuli ($\lambda < 450$ nm), for which minimal spread of the inhibition was observed. Loss of threshold sensitivity is, therefore, most significant for those spectral stimuli which also yield a strong inhibitory effect (fig. 3A). Incremental threshold illumination I_t, for detection of a flashed, 1 deg diameter red (650 nm) target superimposed on a uniform background falls suddenly as the background field illumination reaches a certain non-zero level, for all background field wavelengths (fig. 4 B). Incremental thresholds for other test wavelengths, λ, also show a sudden fall in threshold similar to that observed with the 650 nm test, but for $\lambda \leqslant 600$ nm, it is a relatively small effect (Bender and Ruddock, 1974). Incremental thresholds were also measured for a white light target superimposed on either a red (636 nm) or a white (3000K) background field. Values of log threshold illumination, log I_t, are plotted against log background illumination, log I_b, for subject M. and for the normal subject I.H. The values of log I_t measured with zero background field illumination (log $I_b = -\infty$) are similar, but as log I_b increases, M.'s threshold for the red background increases much more rapidly than I.H.'s. In contrast, the two subjects give similar thresholds for the white background, and the results of fig. 4C therefore confirm that red stimuli produce abnormally large suppression of M.'s sensitivity to test flashes. The data also show that M. has normal sensitivity in response to white light test flashes and background fields. It should be noted that although M.'s thresholds for white light flashes superimposed on a red background are abnormally high, there is no sudden fall in log I_t of the kind shown in fig. 4B. It appears that the highly unusual fall in increment threshold which occurs when the background illumination reaches a certain level is associated solely with the detection of long wavelength test flashes.

Spatial response characteristics of M.'s threshold detection were investigated by several different methods, with particular emphasis on his responses to red lights. Spatial summation for both foveal and non-foveal vision was investigated by

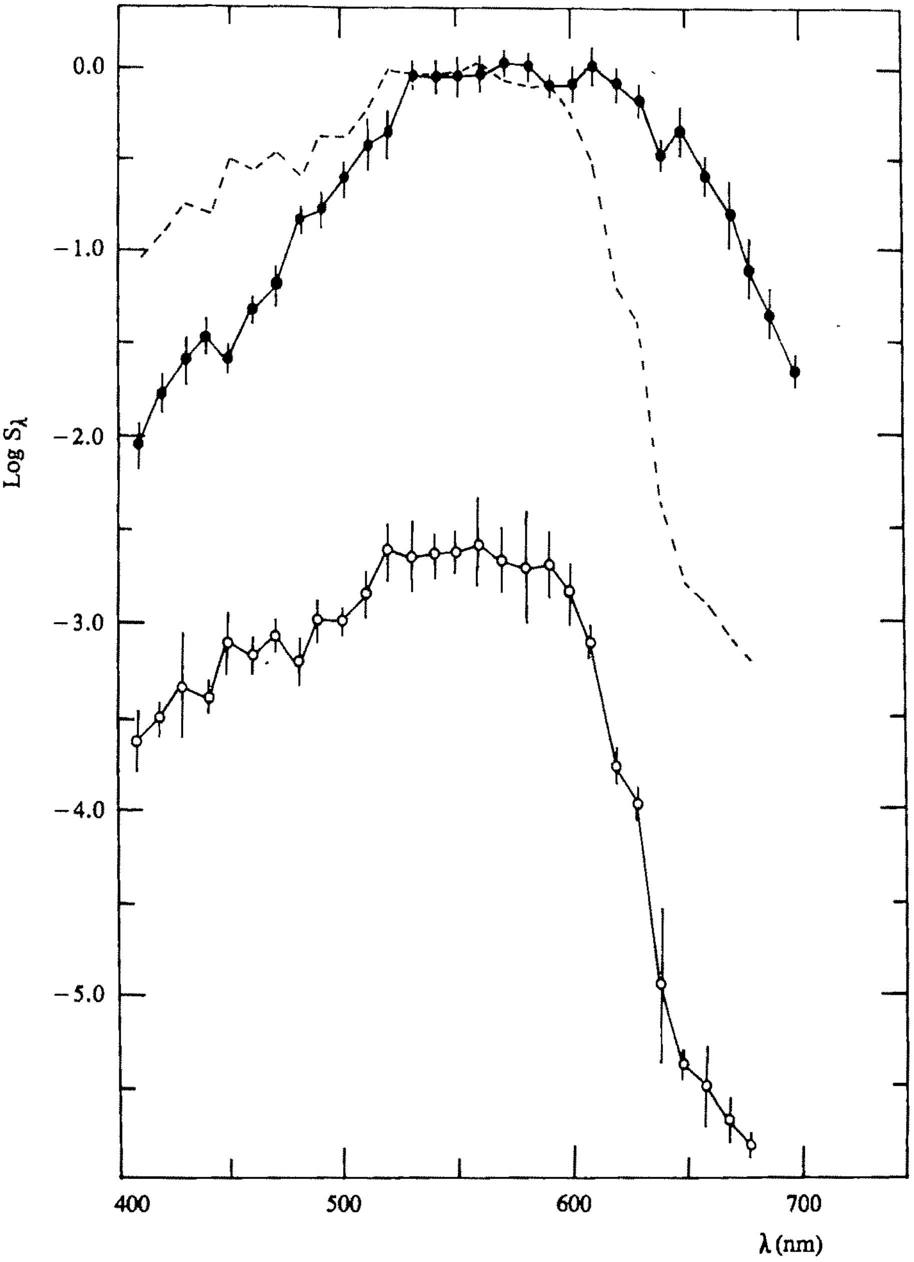

FIG. 4A. Normalized threshold sensitivity values, S_λ, for detection of a foveally fixated, 1 deg circular target of wavelength λ. Sensitivity is expressed as [relative irradiation units]$^{-1}$; open symbols, subject M. closed symbols, normal subject B.B. and the broken line represents M.'s data redrawn for comparison purposes. Error bars show the spread of the three observations made at each wavelength, λ. The target was presented in a ½ s on, ½ s off flash and recovery cycle, and its location marked by four dim white fixation points forming a square around the target.

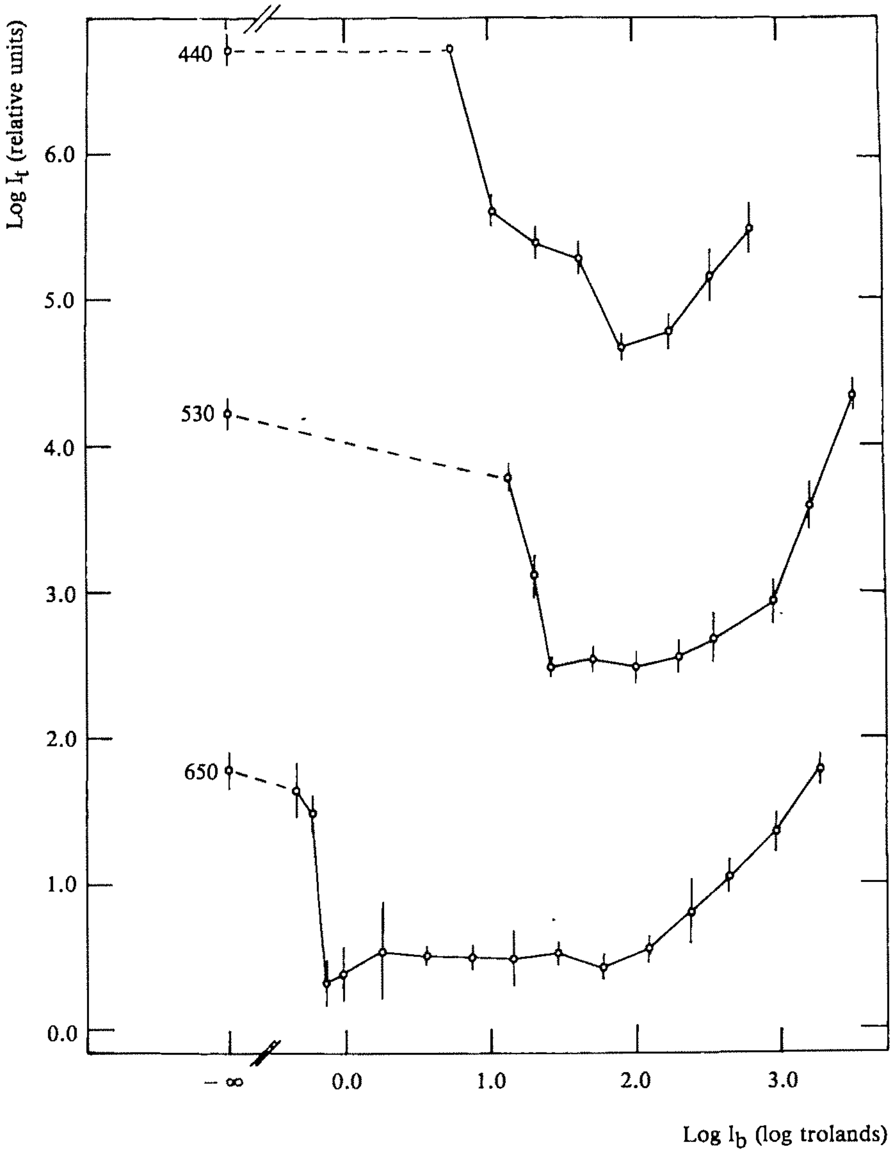

FIG. 4B, increment thresholds, I_t, for detection of a 650 nm, 1 deg circular target superimposed on a concentric 7 deg diameter circular background. The test was presented in a $\frac{1}{2}$ s on, $\frac{1}{2}$ s off cycle against the steady background, of illumination I_b, and data are given for three background wavelengths, as marked to the left of the figure. Data points are the means of three readings with total spread denoted by the error bars. The three curves have been shifted along the log I_t axis for clarity of presentation. Subject M.

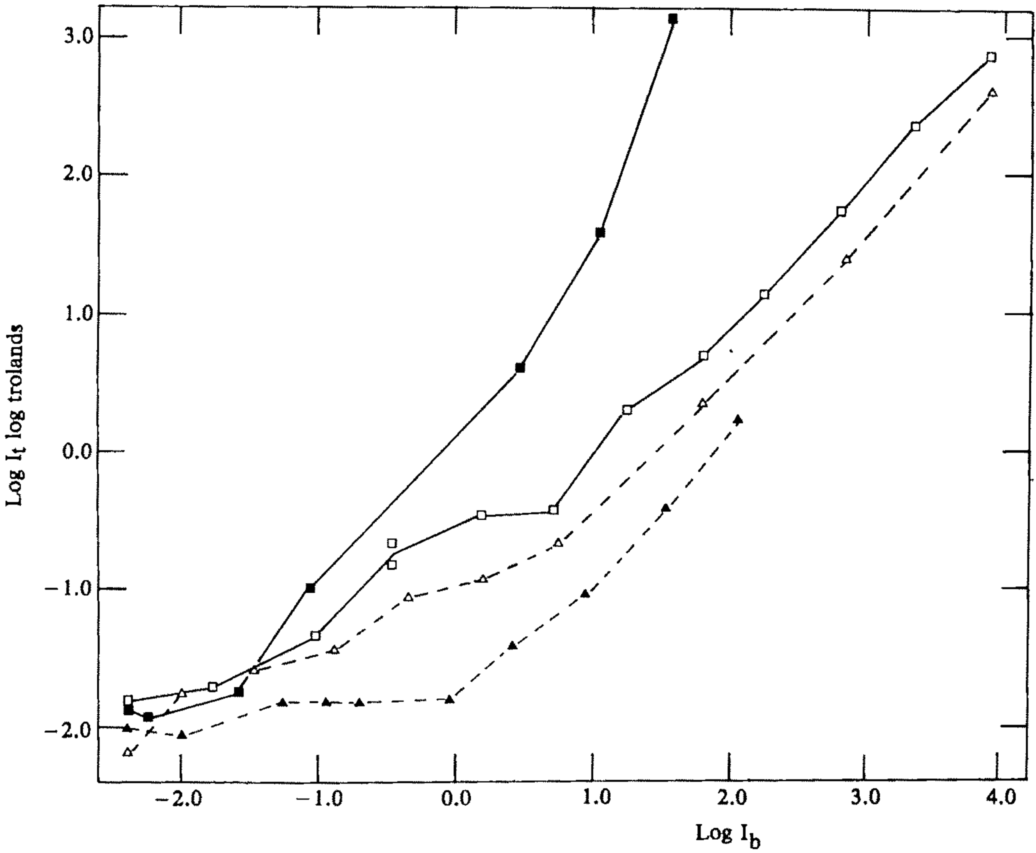

FIG. 4C, threshold illumination, I_t, for detection of a 3.5 deg white light target flashed for 300 ms. once every 3 s, in the centre of a steady, 17 deg background field of illumination level I_b trolands. Full squares, subject M., background wavelength 636 nm, open squares, subject M., white light background; full triangles, subject I.H., background wavelength 636 nm, open triangles, subject I.H., white light background. Each point is the mean of 5 readings, with typical spread of ±0.03 log units.

measurement of threshold levels for 635 nm circular targets of different sizes. The results (fig. 5A) show that neither foveally, nor 30 deg off-axis, is there any significant variation in the values of log I_t. Thus there is no effective spatial summation in the detection of red lights, whereas considerable spatial summation is observed in the spreading inhibition (fig. 3B). Incremental thresholds were measured for detection of a flashed green (524 nm) test target surrounded by a red (636 nm) or green (536 nm) annulus of illumination level I_g, and the results (fig. 5B) show that M.'s detection of the green target is markedly dependent on the illumination level of the surrounding red annulus and to a lesser extent on that of the green, whereas threshold illumination for normal vision (subject I.H.), is virtually unaffected by the red

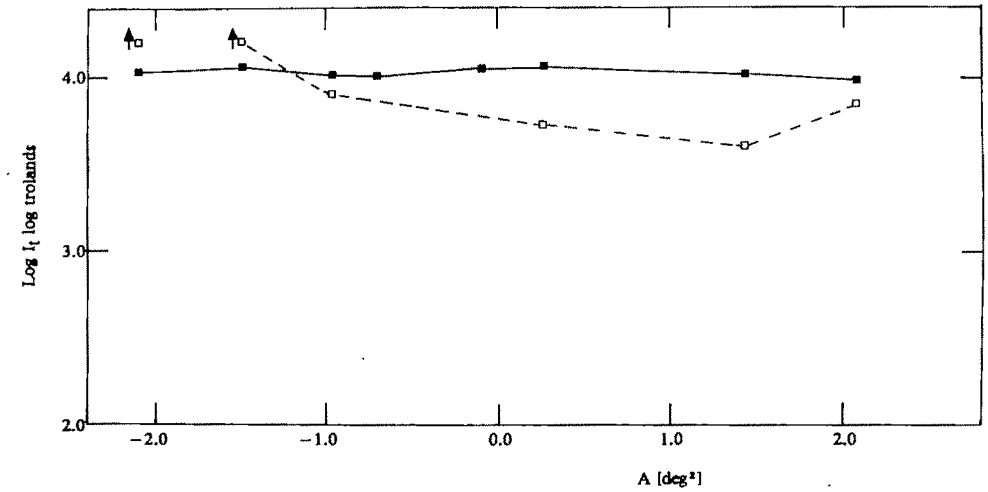

FIG. 5A. Threshold illumination I_t (trolands) for detection of a 635 nm circular target, of area A. The target was presented as a 15 ms flash once every 3 s. Full squares refer to foveal vision and open squares to targets located 30 deg away from the fovea along the horizontal meridian (nasal retina). In the latter case, thresholds for the two smallest targets were greater than the maximum illumination level available (4.2 log trolands). Each point is the mean of 5 readings, with typical spread of 0.03 log units. Subject M.

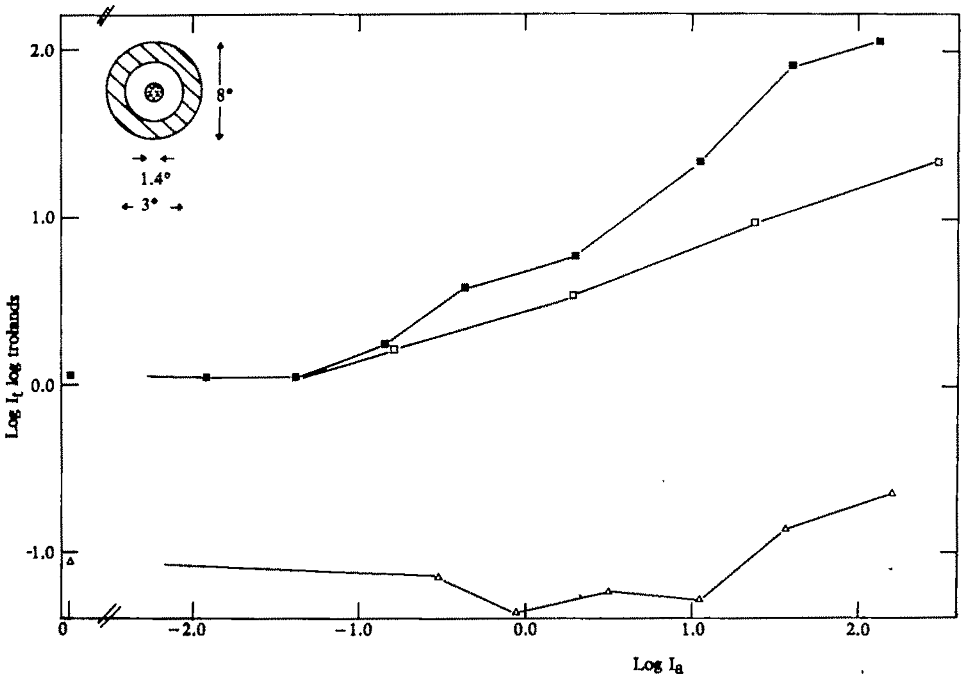

FIG. 5B, threshold illumination level, I_t (trolands) for detection of a 1.4 deg diameter, 524 nm circular target, flashed for 300 ms every 3 s, plotted against the illumination level, I_a, of a concentric annulus (inner diameter, 3 deg, outer diameter 8 deg). Full squares = subject M, 636 nm annulus; open squares = subject M. 536 nm annulus; open triangles = subject I.H., 636 nm annulus. Each point is the mean of 3 readings, with typical spread of ±0.03 log units.

annulus (triangles, fig. 5B). M.'s data correlate with the spreading inhibition illustrated in fig. 1, and confirm quantitatively that red stimuli interfere with detection of targets located in adjacent regions of the visual field, the size of the effect being dependent on the luminance of the red stimulus.

Temporal factors which influence M.'s threshold sensitivity were investigated by flicker fusion and two-flash measurements. The critical fusion frequency for 100 per cent modulated, square-waveform flickering light was measured as a function of its mean illumination level. Similar data were obtained for three stimulus wavelengths, λ, equal to 590 nm, (illustrated in fig. 6A), 500 nm and 440 nm; in each case, M.'s critical fusion frequency saturates at 12 to 15 Hz, whereas for normal vision, it increases continuously with mean illumination level to a value greater than 35 Hz. Red flickering lights caused M. extreme discomfort and he was unable to make observations with such stimuli. This last phenomenon was explored further by the two-flash experiment, in which the threshold illumination level for detection of a 20 ms green (524 nm) test flash was measured as a function of the delay time between the onset of the test and that of a conditioning flash of duration 500 ms. The 17 deg diameter circular conditioning field was concentric with the 1.4 deg diameter circular test flash, and three different conditioning colours were investigated, one

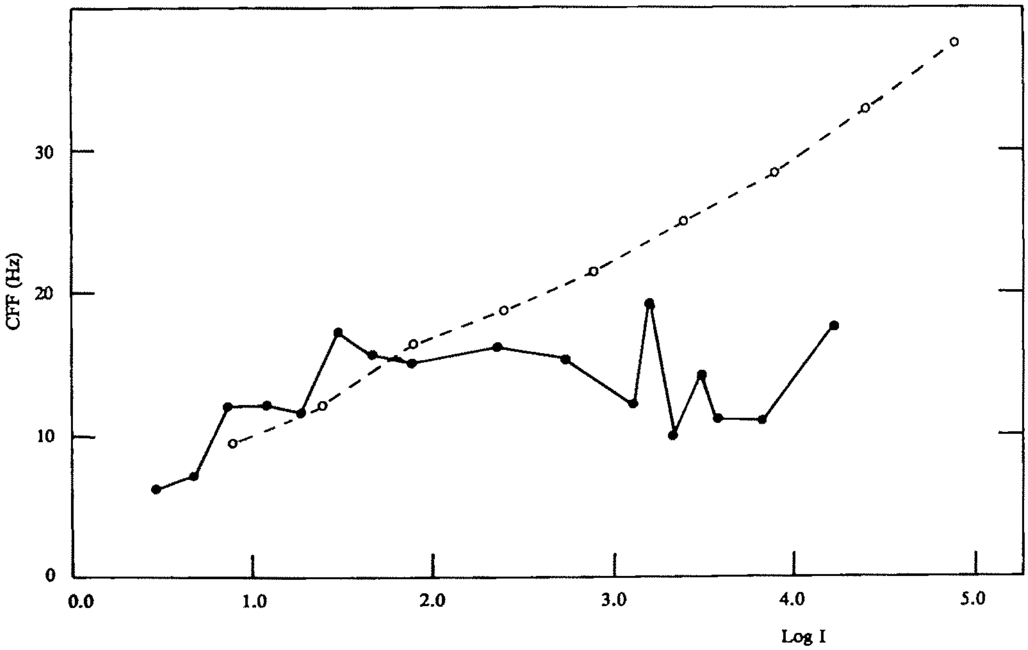

FIG. 6A Critical fusion frequency (Hz) for foveal viewing of a 100 per cent square-waveform modulated, 40 × 80 min, 590 nm test field, of mean illumination level I. Full circles = subject M; open circles = normal subject B.B. Scales of illumination level for the two subjects were adjusted so that log I equal to zero defines threshold level for each subject. Each point is the mean of three readings, with typical spread of 2 to 4 Hz.

red (635 nm), one green (536 nm) and the third white (colour temperature ~ 3000K). The results are expressed as log threshold illumination level plotted against the time delay, τ, between the onset of the two stimuli, with negative values of τ denoting that onset of the test flash precedes that of the conditioning flash (fig. 6B). A red conditioning field of illumination level -1.02 log trolands causes a large increase in M.'s threshold detection level for values of τ in the range -250 ms to 750 ms, and for τ in the range -200 ms to -100 ms, M. was unable to detect the green test flash at the maximum value of log I_t provided by the instrument. Some data are given for a red conditioning field of mean illumination level 2.2 log trolands, but in this case, M. was unable to detect the flash at any value of log I_t provided by the instrument for $\tau \geqslant 0$. The green conditioning flashes influenced the threshold values log I_t to a lesser extent than the red, and the white conditioning flashes gave a very small effect. The data for the normal subject, I.H., exhibit a relatively small variation of log I_t with τ, and his threshold levels for detection of the green flash are much lower than M.'s. The results of fig. 6B demonstrate that M.'s thresholds for detection of the green flash are significantly different in the experiments with coloured conditioning stimuli than in those with white conditioning stimuli. The presentation of test and conditioning stimuli was repeated in a 7 s cycle, until the threshold was set by the subject, and the consistent difference found between the thresholds obtained with chromatic and those obtained with white conditioning stimuli imply that the former produced an increase in threshold maintained during the 7 s cycle. We have not examined systematically this aspect of M.'s responses.

Colour vision. The marked dependence of M.'s visual responses on stimulus colour make it essential to characterize M.'s colour vision as completely as possible. The relevant data have been reported elsewhere (Bender and Ruddock, 1974), but they are reviewed briefly here in order that they can be considered later in relation to the new experimental results.

Wavelength discrimination was determined by finding the wavelength $\lambda \pm \Delta\lambda$ at which M. could just distinguish the colour of one-half of a bipartite 80 min × 80 min field from that of the other half, of constant wavelength, λ. Care was taken to eliminate brightness differences between the two half-fields and the experimental values are plotted in fig. 7A. The data show discrimination steps, $\Delta\lambda$, which are very much greater than those for normal colour vision (Wright and Pitt, 1934; broken line) with a single minimum at about 610 nm. When these data were recorded, the nature of M's spreading inhibition was not appreciated, and both the discrimination and colour matching data (fig. 7B) must to some extent by influenced by the interaction between the two half-fields when one of them is red. None the less, it is clear M.'s wavelength discrimination is seriously impaired, and in confirmation of this, he was unable to identify correctly any but the first of the Ishihara (1976) pseudo-isochromatic plates.

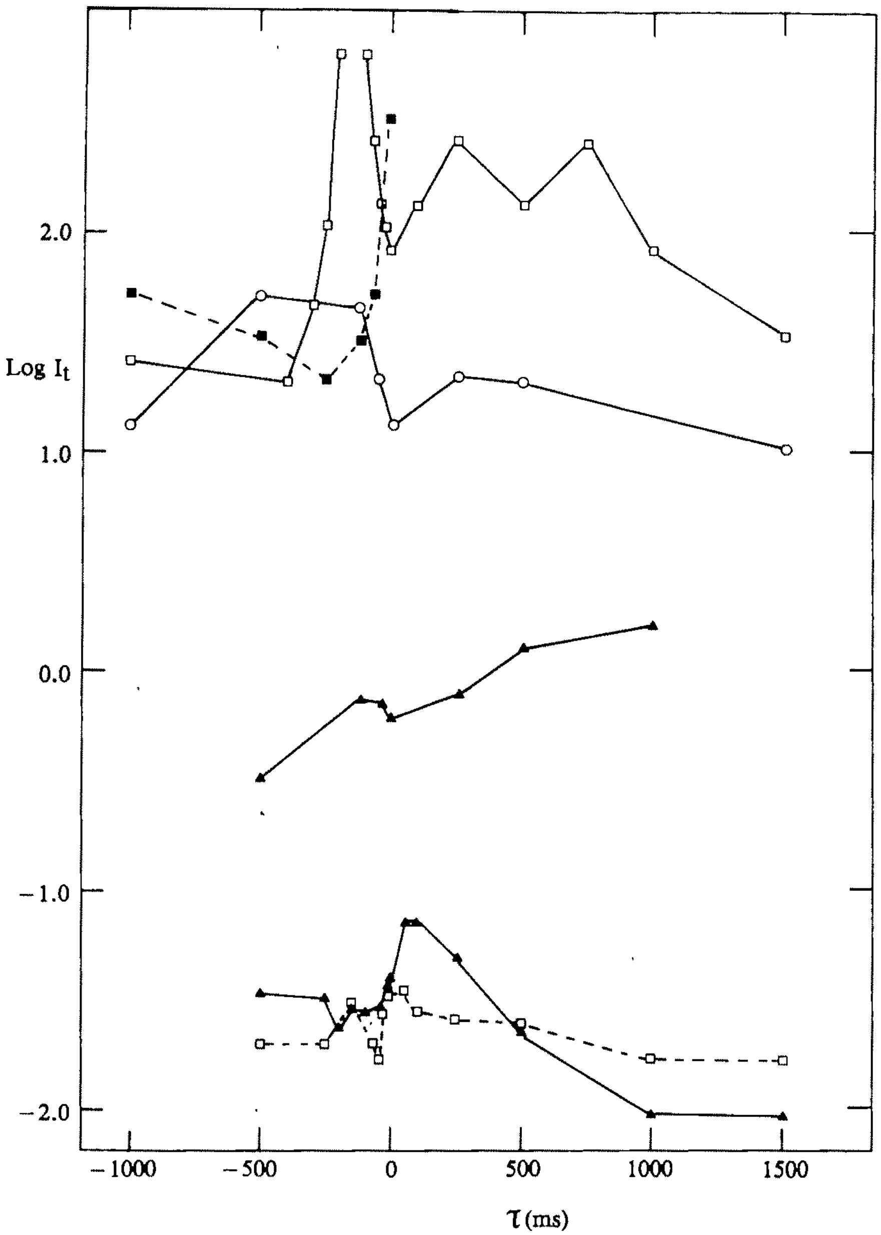

FIG. 6B, threshold illumination level, I_t (trolands), for detection of a 524 nm, 3.5 deg diameter test flash of duration 20 ms. A 17 deg diameter conditioning flash, located concentrically with respect to the test flash, was presented for 500 ms, with a delay τ between the onset of the conditioning and test flashes, the test preceding the conditioning stimulus for negative τ. The two lowest sets of data refer to normal subject I.H., the others to M. Data for subject M: full squares = 636 nm, 2.12 log troland conditioning field; open squares = 636 nm, 1.02 log troland conditioning field; open circles = 524 nm, 1.02 log troland conditioning field; full triangles = white light, 1.1 log troland conditioning field. Subject I.H: full triangles = white light, 1.1 log troland conditioning field; open squares = 636 nm, 1.02 log troland conditioning field. Each point is the mean of 5 readings with typical spread of 0.1 log unit.

Colour matching data were obtained by matching monochromatic test stimuli with a dichromatic mixture of two matching stimuli, one 'red' (600 nm) and one 'blue' (460 nm). The results are expressed as the relative amounts of 'red' and 'blue' required to match a given test wavelength, λ, with the coefficients 'r' and 'b' normalized such that (r + b) is equal to one for each value of λ, and r = b = 0.5 for λ equal to 550 nm. Two sets of values are plotted (fig. 7B); one (circles) refers to a 80 min × 80 min bipartite field and the other (squares) to a 10 deg diameter, circular bipartite field, both fields being centrally fixated. It is clear that M.'s colour vision is similar under both field conditions, which implies that it is uniform over the central 10 deg of the visual field. The match for a white test (colour temperature 2854K) corresponded to that for a monochromatic stimulus of wavelength 578 nm; this defines the 'neutral point' of M.'s dichromatic colour vision.

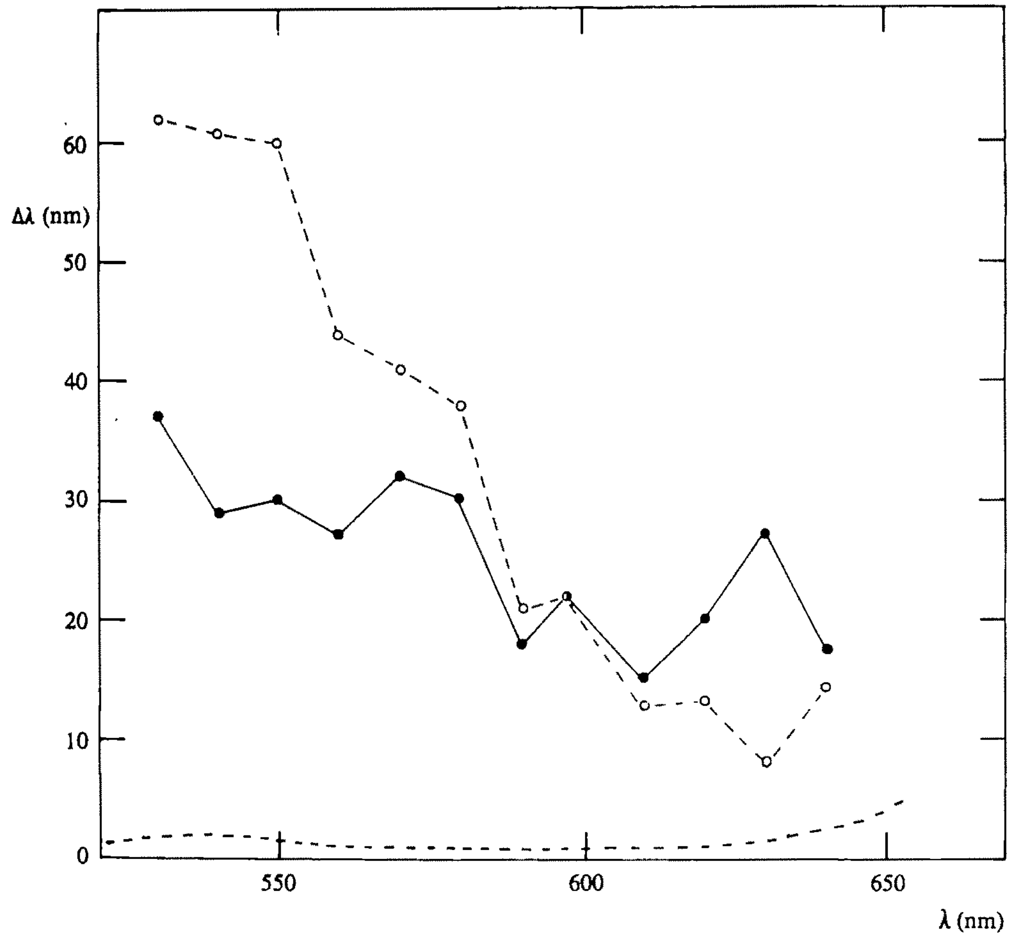

FIG. 7A. Foveal wavelength discrimination, steps, $\Delta\lambda$, measured for a bipartite 80 × 80 min field. Discrimination steps for subject M. are given for reference wavelength, λ, full circles defining values $(\lambda + \Delta\lambda)$ and open circles values $(\lambda - \Delta\lambda)$ at which the two half-fields could just be discriminated. The broken line defines values of $\Delta\lambda$ for normal colour vision (Wright and Pitt, 1934).

Two colour increment threshold data were determined for M. by measurement of thresholds for a 1 deg circular test target of fixed wavelength, μ, superimposed centrally on a uniform background field of variable wavelength λ. The threshold illumination level was first determined for the test field with zero background field and its illumination level then raised by 0.8 log units. Spectral sensitivity functions were measured by finding the irradiation level, E_λ, at which a background field of wavelength λ brought this test stimulus back to threshold, giving a sensitivity S_λ proportional to $(E_\lambda)^{-1}$. Given M.'s unusual increment threshold data (fig. 4B), this method for determination of the spectral sensitivity functions was the only feasible one of the different methods available in normal subjects (Stiles, 1939, 1978). Measurements were made for a number of different test wavelengths, μ, and two spectral mechanisms were isolated. For test wavelengths 590 nm, 551 nm and 495 nm (fig. 7C), the spectral sensitivity function corresponded closely to that of the red-sensitive, π_5, spectral response mechanisms (Stiles, 1939, 1959, 1978). Thus, although the red-sensitive mechanism appears to contribute poorly to detection (fig. 4A), it can be readily identified through its action in suppressing detection of a test flash. The other spectral sensitivity function was isolated by addition of a yellow conditioning field to the background of wavelength λ, a device which enables the

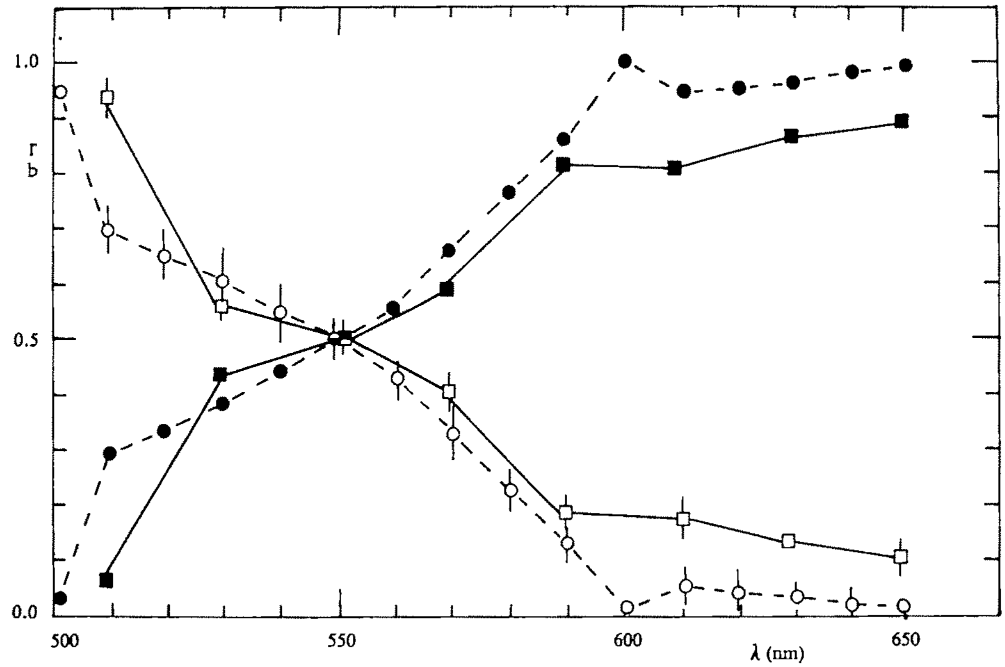

FIG. 7B, colour matching coefficients for a 80 × 80 min bipartite field (circles) and bipartite 10 deg diameter circular field (squares). Matches were established between a monochromatic test field, of wavelength λ, and a dichromatic mixture of a 'red' (600 nm) and a blue (460 nm) matching stimulus. The amounts of red (r) and blue (b) were normalized such that $(r + b) = 1$ and, for λ equal to 550 nm, $r = b = 0.5$. The open symbols give the 'b' coefficients and the closed symbols the 'r' coefficients. Data points are the means of 4 matches, with typical spread indicated by the error bars. Subject M.

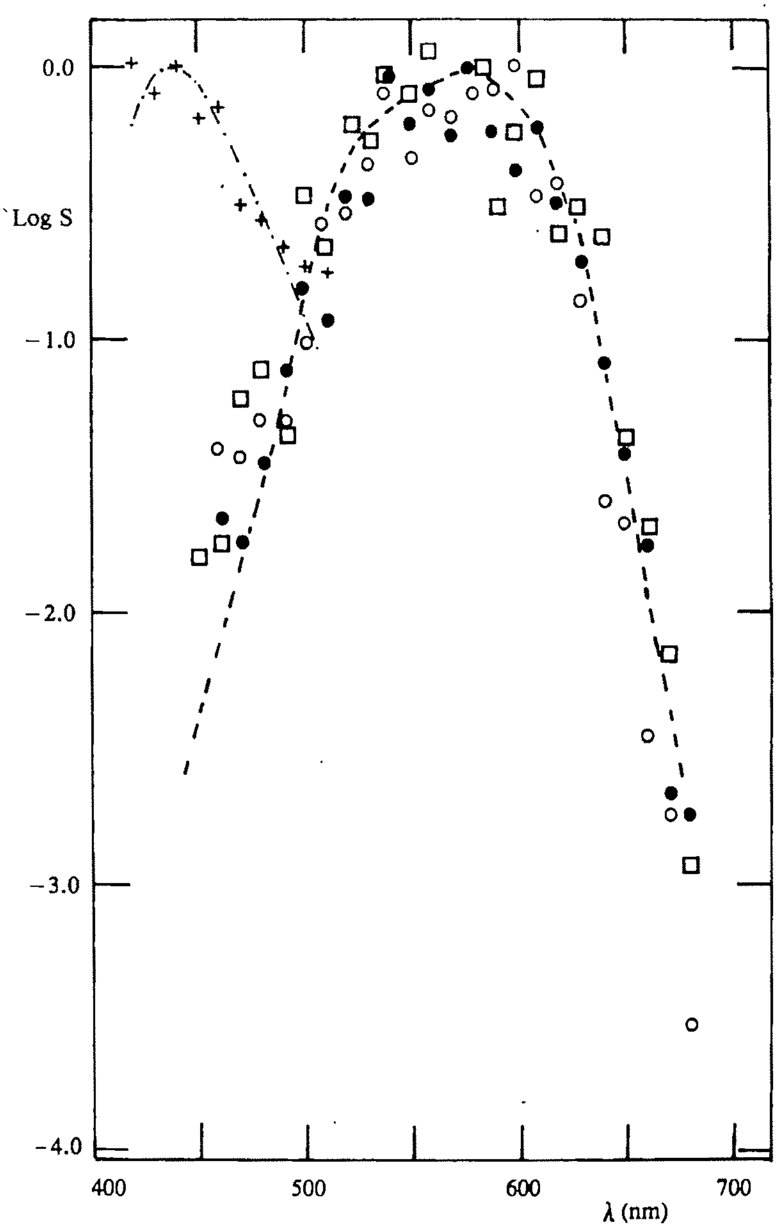

FIG. 7C, spectral sensitivity, S, determined by measurement of the irradiation level of a 10 deg semicircular background field of wavelength λ required to bring a centrally located 1 deg test flash to threshold S, expressed as the inverse of the required irradiation level, is plotted against the background wavelength λ, and the test was set 0.8 log units above threshold, and presented in a $\frac{1}{2}$ s on, $\frac{1}{2}$ s off cycle against the steady background field. Each symbol refers to a different test wavelength μ; open circles = 590 nm; full circles = 551 nm; open squares = 495 nm; crosses = 438 nm, and with a fixed 590 nm, 3 log troland background field added to the variable background. The broken line corresponds to the π_5 and the dash-dot line to the π_1 increment threshold mechanism (Stiles, 1959, 1978). Each point is the mean of three measurements, with typical spread ±0.1 log unit around the mean. Subject M.

blue-sensitive, π_1-mechanism to be isolated. Under these conditions, we observed a blue sensitive mechanism, (fig. 7C), with spectral response characteristics similar to those of the blue-sensitive π_1-mechanism of normal colour vision (Stiles, 1953). More extensive increment threshold data for subject M. have been published elsewhere (Bender and Ruddock, 1974).

Spatial form perception. The preliminary experiments (figs. 1–3) and increment threshold data (fig. 5B) both demonstrate that the abnormal central inhibitory response elicited by red light spreads around the area of stimulation. Quantitative assessment of M.'s form perception under the influence of this central defect was obtained from visual acuity measurements using high contrast ($>$ 98 per cent) one-dimensional, square-waveform gratings as the acuity targets. These were produced as photographic negatives, placed in the Maxwellian optical system and viewed through a 2 mm diameter exit pupil. Resolving power, expressed as the inverse of the grating bar-width, d, which can just no longer be resolved, is plotted as a function of the space-average grating illumination in fig. 8. Values are given for a number of different grating wavelengths, for both M. and a normal subject, V.W. M.'s spatial resolution for long-wavelength stimuli (610 nm and 600 nm) is extraordinarily low, corresponding to bar-widths of 1 deg or a spatial frequency of $\frac{1}{2}$ cycle/deg, and although it improves for shorter wavelengths, he never achieves the normal resolving power illustrated by V.W.'s data. M.'s very low acuity for long-wavelength stimuli was confirmed by measurements with very bright, 100 per cent modulated sine waveform interference fringes derived from a He-Ne laser (output wavelength 632.8 nm). M. could resolve gratings of spatial frequency up to some 0.5 cycle/deg (equivalent to a bar-width of some 1 deg), compared to a value of some 40 to 50 cycle/deg for normal subjects. In white light, M.'s acuity is 6/4 with uncorrected vision, which is comparable to normal, emmetropic vision; thus there is a close correlation between the stimuli for which M. exhibits loss of spatial resolution and those which give rise to the spreading inhibition.

Movement perception. Previous investigation has shown that M.'s responses to moving targets are selectively abnormal for red light. For example, threshold illumination of M.'s detection of 630 nm targets moving at greater than some 30 deg/s is some 3.5 log units greater than that for normal vision; thus target movement does not compensate for M.'s low sensitivity to long-wavelength stimuli (Barbur, *et al.*, 1979). Further, the spatial IMG functions which characterize movement detection in normal subjects (Barbur and Ruddock, 1980*a*, *b*) are grossly abnormal in M.'s detection of moving red targets (Barbur *et al.*, 1979; Barbur, Holliday, Ruddock and Waterfield, 1980).

Central Visual Functions

The experiments with coloured papers showed that spreading inhibition produced by long-wavelength stimuli presented to one eye causes suppression of M.'s sensitivity to targets viewed by the other eye. This implies that central response mechanisms are involved in the inhibition and in this section we report observations on other response functions which provide evidence about the central nature of the defect.

Pupil size was measured as a function of the illumination level of a monochromatic, 3 deg circular stimulus viewed foveally through the Maxwellian projection system. The location of the stimulus was marked by white fixation points, and the stimulus wavelength was varied over the range 656 nm to 570 nm. M.'s pupil responses were similar to those for normal subjects, giving a change from pupil

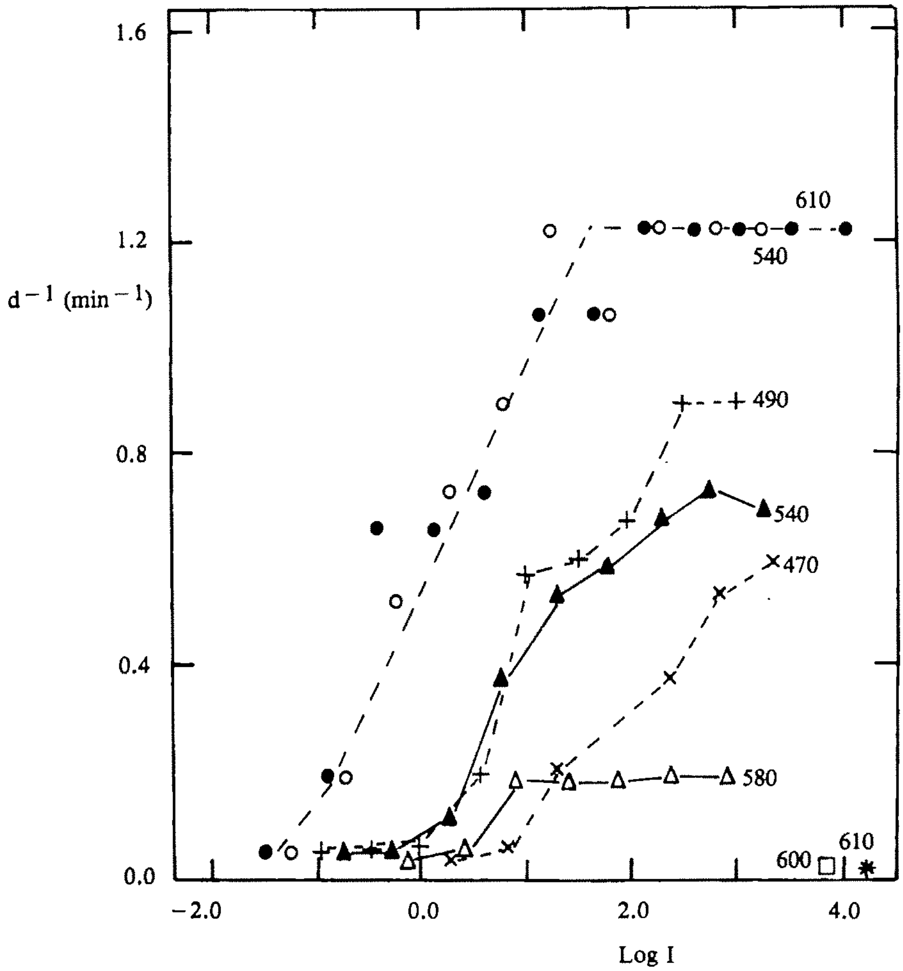

FIG. 8. Grating visual acuity plotted against the space-average illumination level of the grating, I. Acuity is expressed as d^{-1}, where d is the width of the bars in the high contrast (> 98 per cent), square-waveform modulated, vertically orientated grating. The gratings were presented in a 3 deg diameter circular field, and each symbol denotes a different grating wavelength, as indicated to the right of the figure (in nms). The data are plotted such that for a given value of log I, each stimulus wavelength gives the same radiometric flux. Circles refer to the normal subject V. W. (open circles 540 nm and closed circles 610 nm gratings). Other symbols refer to subject M.

diameter 6.0 mm to 4.0 mm for a log unit change in illumination level. The long-wavelength stimuli were as effective for M. as for normal subjects, despite the fact that M. was unable to detect them. We conclude that M.'s pupil reflex does not exhibit low sensitivity to long-wavelength light and is not subject to the abnormal function which leads to very low detection sensitivity. As both the pupil reflex and visual detection are driven by retinal signals, this result suggests that the defect is of central origin.

Stereoscopic depth perception was investigated with Julesz' (1971) random dot anaglyphs printed in red and green inks, which were viewed through red (630 nm) and green (530 nm) interference filters placed one before each eye (*see* Introduction). Observations were made under artificial fluorescent and under normal daylight, with similar results in both cases. When M. looked through the red filter, he could not resolve the single anaglyph elements which subtended some 12 min at his eye, and indeed could not even identify the region of separation between two anaglyphs printed on a single page. His acuity under these conditions was such that he could identify the edge region of high contrast, bar-shaped stimuli of width greater than 2 deg and could detect some variation in contrast for bars of width greater than 1 deg. Viewing through the green filter, M. could resolve the anaglyph elements, although the edges were unclear and the square-shaped elements appeared circular. Viewing through both filters, however, M. was able to identify correctly the stereo-images in either perspective. Anaglyphs including the series with different degrees of correlation between the two images (Julesz, 1971, figs. 8.1.2, A to G), were presented in random order and M.'s general performance was similar to that of two normal subjects, K.R. and V.W., although he was slower in achieving fusion of the stereo-image. With the set of patterns of different correlation, he identified completely the stereo-image at 100 and 90 per cent correlation, but only partially that at 80 per cent. Normal subject K.R. gave similar results, whereas V.W. could identify the 80 per cent completely and could partly identify the 70 per cent correlated image. We attempted to produce responses in normal subjects similar to M.'s by using neutral density filters or diffusing glass to reduce visual acuity, but it proved impossible to reduce grating acuity below 5 cycles/deg (compared with M.'s best performance of $\frac{1}{2}$ cycle/deg in red light), and still fuse the stereo-image. We conclude that M.'s fusion of the stereo-images is not influenced by the spreading inhibition elicited by red stimuli.

Other functions. It has been previously reported (Ruddock and Waterfield, 1978) that for subject M., pattern-dependent binocular interactions can be elicited by long-wavelength stimulus patterns, even though M. fails to detect these patterns. Thus both binocular rivalry and interocular transfer of the contrast threshold elevation effect can be observed in cases where red gratings produce the rival binocular input or the adaptation stimulus, respectively. The new finding that red stimuli produce binocularly transferred spreading inhibition does, however, introduce an additional factor which influences the interpretation of these data.

Thus some of the effects attributed to the pattern specific mechanism may be caused by the general, non-pattern specific inhibitory effect. For example, a large-threshold elevation occurs when M. views a test grating with one eye, following adaptation of the other eye to a uniform field (Ruddock and Waterfield, 1978). In normal subjects, no threshold elevation occurs under these conditions (Maudarbocus and Ruddock, 1973) and it seems probable that in M.'s case, it is a result of the abnormal inhibitory effect.

DISCUSSION

In the results section, we have presented data which describe the principal characteristics of M.'s visual responses. It has been shown that M. makes consistent and accurate, albeit grossly abnormal, threshold settings and colour matches, and we conclude, therefore, that we are dealing with a disturbance of the visual sensory pathways, rather than with some more central abnormality leading to a 'psychological' block in response to certain stimuli. In this section, we will examine first the nature of M.'s colour vision, which is of importance to the remaining discussion. We then discuss M.'s visual responses in relation to theories of visual organization, and in so doing, we assume that M. suffers a specific dysfunction arising in visual pathways organized broadly in the normal way. The alternative view, that his visual system is generally abnormal in its organization, seems unlikely to be valid as there is no evidence that the defect is congenital.

The nature of M.'s colour vision. M.'s sensitivity in detection of long-wavelength lights is very low (fig. 4A), but red light has considerable inhibitory effect on his vision (fig. 3B, C) and the activity of the red sensitive (π_5) mechanism in setting increment threshold values is clearly shown in fig. 7C. It is important to note that despite his low sensitivity in detection of long-wavelength lights, M. does *not* suffer from a form of protanopia, the congenital red-green colour vision defect caused by absence of the red-sensitive photopigment (Rushton, 1963). Thus protanopes are insensitive to red lights, whether used as test or background stimuli, they do not exhibit the red-sensitive (π_5) increment threshold spectral mechanism and their well-defined dichromatic colour vision, with the neutral point at about 495 nm (Pitt, 1944), is completely different from M.'s with the neutral point at about 580 nm (fig. 7B). Further, no studies on protanopes have ever revealed a spreading inhibitory function associated with detection of red stimuli. None the less, we made check measurements with a protanope (an 18-year-old male, D.C.), with test cards of the kind illustrated in fig. 2A, the colours being selected as those which elicit the greatest inhibitory response in subject M. D.C.'s detection of the high contrast targets was completely uninfluenced by the coloured patches, confirming that the principal feature of M.'s vision cannot be ascribed to protanopia.

In the Methods section, we pointed out that there are cases of red-green congenital colour vision deficiencies in both M.'s maternal and paternal families.

Thus, the nature of M.'s underlying retinal colour vision mechanisms are open to question. His mother is not defective, but must be a carrier, as a sister is red-green defective. M. may, therefore, have inherited normal colour vision or a red-green deficiency. Both M.'s colour matching and increment threshold data indicate dichromatic colour vision resting on activity of the red (π_5) and blue (π_1) sensitive mechanisms. The colour matching, however, must be treated with caution because the spreading inhibition gives rise to interaction between the two half-fields, and the strong inhibition associated with long-wavelength stimuli could cause distortion of the increment threshold data. The marked colour specificity of the inhibitory interaction (fig. 3A) shows clearly that yellow and green colours give quite different responses from reds; thus M. cannot be a red-green dichromat, for whom all stimuli in the red-yellow-green spectral range are equivalent (*see* Pitt, 1944). M. must, therefore, possess retinal mechanisms which yield either anomalous trichromatic or normal colour vision; the fact that yellow, unlike all other spectral stimuli but like white, produces no inhibitory effect, suggests that yellow is closest to white, that is, it is the most desaturated of the spectral colours. We regard this as strongly indicative that M.'s retinal colour vision mechanisms are normal, because for subjects with normal colour vision, yellow is the least saturated spectral colour (*see* Wright, 1946) whereas for those with anomalous trichromacy, wavelengths in the range 530 nm to 600 nm are equally desaturated (Nelson, 1938; McKeon and Wright, 1940).

The site of M.'s spreading inhibition. The stimulus specificity of the inhibition, which is elicited strongly by red lights, weakly by greens and blues, but not at all by yellow and white lights, eliminates the possibility that it arises as a consequence of absorption in a given spectral class of cone photopigment. Thus white light is absorbed significantly by all spectral classes of cone, but does not produce the inhibitory response. This conclusion is confirmed by the observation that a normal pupil reflex is elicited by red lights, which implies that the retinal signals which travel to the pre-tectal region of the midbrain are not influenced by the inhibitory effect. The observations with two-colour random dot anaglyphs establish that the defect arises centrally relative to the point at which signals from the two eyes interact. Electrophysiological recordings from the macaque show that signals from the two eyes first converge to give binocular control of single neurons at cortical level (area 17), (Hubel and Wiesel, 1968) and we conclude that the inhibitory effect which suppresses M.'s detection of the red anaglyph, but which does not effect his stereo-fusion, arises centrally relative to the level of binocular fusion in area 17. The conclusion that the inhibitory effect is of central origin is consistent with its dichoptic transfer observed in the preliminary experiments (*see* Results section).

All spectral stimuli elicit some abnormal visual responses, but in contrast, white light gives normal responses. This is exemplified by the threshold detection of test flashes, where all spectral stimuli yield low-threshold sensitivity values (fig. 4A), whereas white light gives a threshold level similar to that for normal vision (fig. 4D). The defect is thus associated with response mechanisms involved in the processing of chromatic signals, and an obvious candidate for the site of the defect is pre-striate area V4, the neurons of which are largely (60 per cent) colour selective in response (Zeki, 1978). Although receptive fields of single neurons in area V4 can be large (some 5 deg square, Zeki, 1980), they are not as extensive as is implied by the spatial summation observed in the spreading inhibition (fig. 2B). Further, mapping of the visual field on to area V4 is restricted to the contralateral half-field, except for a 1 deg strip around the vertical meridian (Zeki, 1970), whereas the inhibition spreads across the vertical meridian over at least 4 deg into the contralateral half-field; thus mechanisms more central than area V4 must also be involved.

We have considered the possibility that M.'s abnormal inhibitory response may arise in the retinal projections to the superior colliculus rather than in the geniculostriate pathways. This can be tested by comparing M.'s response characteristics with those of a hemianopic subject, for whom detailed responses to stimulation of the 'blind' hemifield have been reported (Barbur, Ruddock and Waterfield, 1980). Similarities between data for the two subjects include low flicker fusion frequency, low sensitivity in detection of flashes, and large spatial summation both in detection of flashes for the hemianope and in M.'s response to inhibitory stimuli (fig. 2B). There are, however, other responses which differ markedly between the two subjects. Thus M.'s inhibitory response is observed only with spectral stimuli whereas the hemianope's blind-field responses are readily observed with white light and show little colour selectivity. Further, M. exhibits no spatial summation in the *detection* of red test flashes located either centrally or 30 deg off-axis (fig. 5A) whereas the hemianope exhibits very extensive spatial summation in detection 30 deg off-axis. Finally, no inverse Fechner fraction effect is observed in the hemianope's increment threshold settings. On balance, the evidence does not strongly support the hypothesis that M.'s abnormal responses are associated with the same pathways as those which gave rise to 'blind-field' vision in hemianopes (Weiskrantz, Warrington, Sanders and Marshall, 1974; Barbur, Ruddock and Waterfield, 1980).

Central representation of colour. M.'s responses provide an unusual opportunity to examine the properties of visual signals which carry chromatic information. In all functions examined, including visual acuity (fig. 8), threshold sensitivity (fig. 4), movement detection and the inhibitory effect itself (fig. 3), M. responds normally to white light stimuli and more or less abnormally to chromatic stimuli. Thus M.'s response characteristics provide clear evidence for separation of chromatic from achromatic information by the visual system. The evidence that M.'s stereo-function of random spot anaglyphs is not disturbed by the inhibitory defect associated with chromatic stimuli is consistent with Lu and Fender's (1972) finding that such fusion involves luminance but not chromatic contrast signals. M.'s experimental data show that the magnitude of the inhibitory effect elicited by chromatic stimuli increases as the stimulus luminance increases (figs. 3B, 5B), thus the chromatic channels responsible for the effect must convey information about the stimulus luminance, and not simply about the chromaticity (x, y values) of the stimulus. In principle, it should be possible to analyse the physiological representation of desaturation on the basis of the equation given in the Appendix and the data of figs. 3B, C, but unfortunately, the data of fig. 3B are insufficient for this purpose, and with the equipment presently available to us, we could not obtain more extensive values.

Visual representation of different stimulus parameters. We have provided evidence that M. has a visual defect of central origin, associated specifically with the detection of coloured stimuli. Recent anatomical and electrophysiological studies on the macaque have demonstrated multiple cortical mapping of the visual field, with neurons located in a given visual area responding selectively to a single stimulus parameter (Zeki, 1978). We have already made reference to the colour-selective nature of neuronal responses in visual area V4, and have identified it as a possible site of origin of M.'s spreading inhibition. The existence of stimulus response selectivity associated with different cortical maps can be interpreted as evidence for separate cortical processing of the various stimulus paramerers such as colour, movement and spatial form. It is therefore of interest to examine the extent to which M.'s colour specific central defect influences his responses to other stimulus parameters. It is clear that for long-wavelength stimuli, stimulus movement, spatial resolution (fig. 8) and spatial form perception (fig. 1) are all disturbed, whereas fusion of random spot stereo-images is normal, as are the other three functions for white light stimuli. Thus there appear to be connections between the chromatic channels and those which process movement and spatial pattern detection, through which the inhibitory effect is transmitted. The disparity sensitive channel responsible for the fusion of random spot stereo-images is apparently independent of the chromatic channel (Lu and Fender, 1972) and is not influenced by the inhibitory effect.

SUMMARY

This paper deals with a single male subject, M., who has a well-defined visual defect of a kind not previously described. The defect is associated with a potent inhibitory response to long-wavelength stimuli, which spreads for up to 12 deg from the area of stimulation, suppressing M.'s detection of other high contrast stimuli. The effect can also be observed, weakly, with certain other coloured stimuli, but not with yellows or whites. Detailed psychophysical data are given for threshold sensitivity, colour matching, two-colour increment thresholds and visual acuity, all of which are more or less abnormal, depending on the stimulus colour. No abnormal effects were, however, observed with white light stimuli. On the basis of M.'s ability to fuse red and green random dot stereogram pairs, we argue that the inhibition arises centrally in the visual pathways, and we examine the implications of M.'s response characteristics for the analysis of central visual processing.

APPENDIX

In order to express the influence of stimulus saturation on the inhibition effect, we derive the luminance, Y_s, of the chromatic component of the desaturated stimulus. Assume that desaturated colours are represented by a combination of white, represented by chromaticity co-ordinates (x_w, y_w) and a saturated colour, represented by the chromaticity co-ordinates (x_s, y_s). Consider a desaturated colour with chromaticity (x, y) and luminance Y. Then if the tristimulus values of the white and saturated stimuli which, when mixed, produce the desaturated colour are, respectively, X_w, Y_w, Z_w and X_s, Y_s, Z_s, then:

$$(1)\quad x_w = \frac{X_w}{(X_w + Y_w + Z_w)}; \qquad y_w = \frac{Y_w}{(X_w + Y_w + Z_w)}$$

$$(2)\quad x_s = \frac{X_s}{(X_s + Y_s + Z_s)}; \qquad y_s = \frac{Y_s}{(X_s + Y_s + Z_s)}$$

and

$$(3)\quad x = \frac{(X_w + X_s)}{(X_w + Y_w + Z_w + X_s + Y_s + Z_s)}; \qquad y = \frac{(Y_w + Y_s)}{(X_w + Y_w + Z_w + X_s + Y_s + Z_s)}$$

From (1), (2) and (3)

$$(4)\quad \frac{x_w}{y_w} = \frac{X_w}{Y_w} = K_w; \qquad \frac{x_s}{y_s} = \frac{X_s}{Y_s} = K_s$$

and

$$\frac{x}{y} = \frac{(X_w + X_s)}{(Y_w + Y_s)}, \text{ giving from (4): } \frac{x}{y} = \frac{(Y_w K_w + Y_s K_s)}{(Y_w + Y_s)}$$

but $Y = (Y_w + Y_s)$

$$\text{therefore } \frac{x}{y} = \frac{[(Y - Y_s)K_w + Y_s K_s]}{Y}$$

that is,

$$(5)\quad Y_s = Y \frac{[x/y - K_w]}{[K_s - K_w]}$$

For samples of constant luminance which lie on a straight line between the white point and a fixed point on the spectrum locus, Y, K_s and K_w are all constant, thus Y_s is proportional to x/y and gives a measure of the saturation of the samples. If, physiologically, desaturated stimuli gave rise to two signals, one chromatic ('saturated') and the other achromatic ('white'), Equation 5 would define the magnitude of the former.

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(*Received May 7, 1981*)

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BRAIN-STEM AUDITORY-EVOKED POTENTIALS RECORDED DIRECTLY FROM HUMAN BRAIN-STEM AND THALAMUS

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INTRODUCTION

FAR-FIELD averaging techniques have in the last few years been used widely to record auditory and somatosensory averaged evoked responses from the scalp, remote from their presumed sources. Brain-stem auditory-evoked potentials (BAEP) have been shown to be of value for the localization of brain-stem lesions (Starr and Achor, 1975; Stockard and Rossiter, 1977; Hashimoto, Ishiyama and Tozuka, 1979); the diagnosis of multiple sclerosis (Robinson and Rudge, 1977); evaluation of the neurological status of comatose patients (Starr and Achor, 1975); the diagnosis of brain death (Starr, 1976), and monitoring of the brain-stem function in the operating room (Hashimoto, Ishiyama, Tozuka, Mizutani, 1980); and are now routinely applied for objective auditory screening in neonates and children who are untestable by behavioural methods (Sohmer and Feinmesser, 1973; Hecox and Galambos, 1974; Galambos and Galambos, 1975).

The BAEP components have been studied in animals by depth recordings with either macro-electrodes (Jewett, 1970; Lev and Sohmer, 1972; Achor and Starr, 1980*a*) or micro-electrodes (Huang and Buchwald, 1977) and by making lesions (Buchwald and Huang, 1975; Achor and Starr, 1980*b*). In these studies, five components were identified and attributed to specific intracranial sources (Lev and Sohmer, 1972; Buchwald and Huang, 1975), although a significant overlapping of the activities was present (Jewett, 1970; Huang and Buchwald, 1977; Achor and Starr, 1980*a*). By contrast, the sources of the components of human BAEP remain inconclusive in spite of numerous correlative studies in patients with lesions of the brain-stem at various levels (Starr and Hamilton, 1976; Stockard and Rossiter, 1977; Hashimoto *et al.*, 1979).

Because these potentials represent the only available indicator of the neural mechanisms that underlie human auditory processes in the brain-stem and also provide a powerful means for non-invasive investigation of patients with brain-stem dysfunctions, precise information of the sources of each BAEP component in man would be of the utmost importance. Direct intracranial recordings are required for this purpose. However, few direct recordings from the human brain-stem have been carried out (Hashimoto *et al.*, 1980) and the information obtained has been fragmentary. Accordingly, we have recorded the potentials directly from the VIIIth nerve, brain-stem, thalamus and cortex during neurosurgical procedures, in order to delineate the generators of each BAEP component recorded through the scalp.

METHODS

Recordings from surface electrodes overlying the VIIIth nerve, brain-stem, thalamus, and cerebellar and cerebral cortices were carried out in 19 patients during surgical treatment of intracranial disease. Recordings from the thalamus were also taken in a patient during stereotaxic surgery for the alleviation of thalamic pain. The presumed anatomical location of the electrode in the thalamus was determined by using Schaltenbrand and Bailey's Atlas (1959).

In 3 patients, recordings were obtained from the IVth, IIIrd and lateral ventricles, as well as subcortical and cortical structures during ventricular catheterization through a frontal burr hole for diagnostic purposes. Two patients underwent both ventricular catheterization and surgical treatment and recordings were taken during both procedures (Table 1). Surface recordings were obtained by the use of a silver ball electrode 0.5 mm in diameter with an insulated flexible silver wire lead (0.1 mm in diameter) which was held in place by applying a small cotton patty soaked in normal saline over the silver ball; for intraventicular recordings, this electrode was passed through the ventricular catheter so that only the ball electrode protruded from the end of the catheter to record the potentials from the ventricular system.

General anesthesia with halothane and nitrous oxide was used in 19 patients and local anesthesia (1 per cent Procaine) in other patients. Throughout all the stages of the recording procedure, the basic principles of the Declaration of Helsinki (1964) concerning human experimentation were followed.

TABLE 1

Lesions	*No. of cases*
Aneurysms of the vertebrobasilar system	5
AVM of the upper vermis	1
Medulloblastomas	2
Pinealomas	2
Acoustic neurinomas	3
C-P angle meningioma	1
C-P angle epidermoid	1
AVM of the IIIrd ventricle	1
Fisher's syndrome	1
Dejerine-Roussy syndrome	1
AVM of the frontal lobe	1
AVM of the parietal lobe	1
Astrocytoma of the parietal lobe	1

AVM = arterio-venous malformation. C-P angle = cerebello-pontine angle.

The reference electrode for intracranial recordings was an alligator clip clamped on the muscle at the edge of the craniotomy. In each recording session, one record was taken from a constant scalp electrode placement (C3-A1 or C4-A2 derivation) in order to assess the stability of the recordings and to correct for the possible latency shifts that may occur with varying degrees of hypothermia and depth of anesthesia as well as those associated with pre-existing brain-stem dysfunctions.

We limited each recording session to a maximum of 30 minutes during surgery.

Electrode impedance was measured and maintained at a level less than 3K ohms. The input signals from the intracranial and scalp electrodes were amplified by a physiological amplifier (Nic-HGA-100) with a gain of 10^4 and a frequency response down 3 dB at 30 and 3 kHz. As a rule, the responses to 1000 click stimuli were averaged for 10 ms at a sampling rate of 20 μs employing a Nicolet Ca-1000 averager. The averages were written out on an X-Y plotter in which positivity of the active electrode was down in all recordings. The latency of the responses was determined by selecting on the oscilloscope the appropriate memory address.

Rarefaction clicks (0.1 ms) were generated by a Nic-1001 click generator and delivered to TDH-39 transducers mounted in acoustically shielded cushions or commercially available insert earphones. Their intensity was 65 dB above threshold for each patient and the usual presentation rate was 15/s. For several recording sessions a Medelec MS6 averaging computer was also used and in such occasions, the time base of 9 ms was employed.

RESULTS

1. *Cochlear nerve*

Two surface electrodes were placed on the cochlear nerve; one on the intrameatal part and another on the extrameatal part 10 mm proximal to the internal auditory meatus. Three patients were examined during posterior fossa operations. The potentials showed significant changes in peak latencies and amplitudes depending on the electrode sites. However, waveform and relative timing of the response components were similar in all the patients. Following click stimulation, the potentials from the intrameatal part of the cochlear nerve were 2 positive (P1 and P2) and 2 negative (N1 and N2) components in which the initial negative component (N1) was dominant (19 to 52 μV). The latency of onset of the initial positive component (P1) ranged from 1.35 ms to 1.5 ms. The ranges of peak latencies for the components were: P1, 1.73 to 1.8 ms; N1, 2.32 to 2.92 ms; P2, 2.88 to 3.6 ms; and N2, 3.24 to 4.2 ms. On the other hand, the potentials recorded from the extrameatal part consisted of a positive and a negative wave. The peak latency of the positive wave ranged from 2.4 to 2.95 ms and of the negative wave, 3.08 to 3.59 ms. The amplitude of the negative component was approximately one-third that of N1 from the internal auditory meatus. By measuring the time difference between the two negative peaks, the conduction velocity of the cochlear nerve between the two electrode sites was calculated and was found to be approximately 13 m. s^{-1}.

Since the action potentials direct from the cochlear nerve were extremely large, they could be clearly seen in single sweeps. The amplitude of N1 was relatively resistant to the effects of increasing stimulus repetition rate. In fact, this component could be recorded at 100 per cent of its maximum amplitude at a stimulus repetition rate up to 20 Hz. However, it reduced to 70 and 50 per cent at a repetition rate of 50 Hz and 100 Hz, respectively, and virtually reduced to 0 per cent at 200 Hz. The finding is comparable to the amplitude decrement of wave I over the scalp with increasing click repetition rate (Chiappa, Gladstone and Young, 1979).

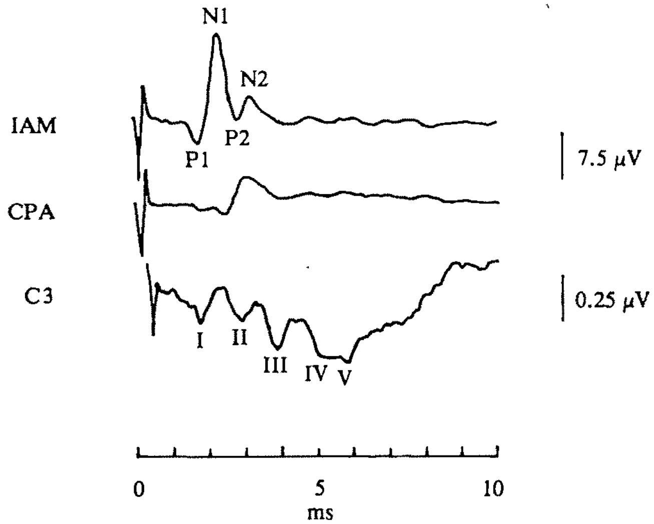

FIG. 1. Comparison of brain-stem auditory-evoked potentials recorded from the scalp and the VIIIth nerve to click stimulation. Note different calibration and larger amplitude of the VIIIth nerve responses. The onset and peak of the initial positive component from the intrameatal portion of the nerve are synchronous with those of wave I at the scalp, while the following large negativity is almost concurrent with the negative component between waves I and II. The second negative component and also the initial positive and negative components from the extrameatal portion of the VIIIth nerve have latencies within the range of wave II. C3 indicates responses obtained from C3 with a reference to A1. IAM and CPA = the VIIIth nerve potentials recorded within the internal auditory meatus (IAM) and the region of the cerebello-pontine angle (CPA), respectively.

Recordings from the cochlear nerve were compared with those from the scalp (fig. 1). The onset (1.35 ms) and peak (1.76 ms) of the initial positive component (P1) from the internal meatus were coincident with those of scalp wave I. The large negative component (N1) which follows P1 had a peak latency (2.32 ms) almost concurrent with that of the initial scalp negative component between waves I and II. The second positive (2.88 ms) and negative (3.24 ms) waves had latencies within the range for wave II. Similarly, the initial positive (2.4 ms) and negative (3.08 ms) components from the extrameatal portion of the cochlear nerve had the latency range of wave II. It is therefore reasonable to assume that wave I recorded from the scalp with the earlobe reference reflects the earliest action potentials (N1) generated from the most distal portion of the cochlear nerve which is inaccessible under normal conditions.

2. *Brain-stem*

Evoked potentials to click stimulation were recorded extensively over the surface of the brain-stem from the medulla to the midbrain. The waveform of the potentials varied at different recording sites. The potentials recorded over a given anatomical location, however, were fairly similar from one subject to another.

Within the region of the medulla oblongata (dorsal surface) three positive components could be identified; the earliest P1 component had a peak latency of 1.8 ms, the second P2 component 2.8 ms and the third component 3.8 ms (fig. 2). The peak latencies of the three components correspond in time to those of waves I, II and III. However, these potentials recorded from the medulla cannot be considered to arise from the medulla itself but may represent volume-conducted far-field potentials from other sources, since their absolute amplitudes (less than 0.4 μV) are so small, and, more important, they are not significantly changed in amplitude by moving the electrode position over the region of the medulla.

In contrast, the potentials from the pons and midbrain were much increased in size compared with recordings from the medulla and they were changed markedly in waveform and amplitude by a small displacement of the recording electrode. Recordings were taken from the dorsal surface of the pons and inferior colliculus in 3 patients whose IVth ventricle was opened during the course of posterior fossa

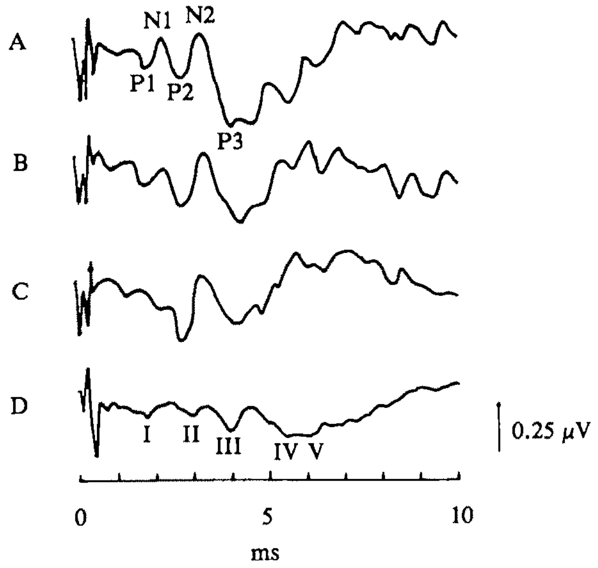

FIG. 2. Brain-stem auditory-evoked potentials recorded from dorsal surface of the medulla oblongata and the left VIIIth nerve to right monaural stimulation. A = recordings from left VIIIth nerve. B = left nucleus gracilis. C = obex. D = scalp recording from C4 with a reference to A2. Three positive components from the contralateral VIIIth nerve and nucleus gracilis and obex correspond in time to scalp recorded waves I, II and III. Since their amplitudes (less than 0.4 μV) are too small and virtually unchanged by electrode displacement, except for P1 which is much more attenuated at the obex, they may represent volume-conducted potentials from other distant sources.

explorations. Two surface electrodes were placed under an operating microscope, one over the midline of the pons at the level of the facial colliculus (vicinity of the trapezoid body) and another over the inferior colliculus (fig. 3A). Three prominent positive components (P2, P3 and P4) separated by two negative deflections (N2 and N3) were recorded from the electrode overlying the trapezoid body (fig. 3B). Two additional positive wavelets were superimposed on its falling phase of a relatively slow negative potential (N4). In recordings from the inferior colliculus a large slow positive component (P5) predominated, and the earlier waves were considerably attenuated. This P5 component is a virtual mirror-image of the slow negative component in the recordings from the pons. This indeed suggests that the potential source is close to the recording electrodes.

Although there was a small peak latency difference (0.3 ms) between wave V and the P5 component from the inferior colliculus, wave II and III showed close correlation with the P2 and P3 components from the midpons. The amplitudes of the BAEP over the scalp were from one-twelfth (wave II) to one-twentieth (wave V) of their maximum amplitudes at the brain-stem.

Direct recordings from other patients were essentially similar in wave-forms and latencies. Fig. 3C shows another example of recordings from the identical loci in the brain-stem. Evoked potentials from the midbrain were dominated by a large

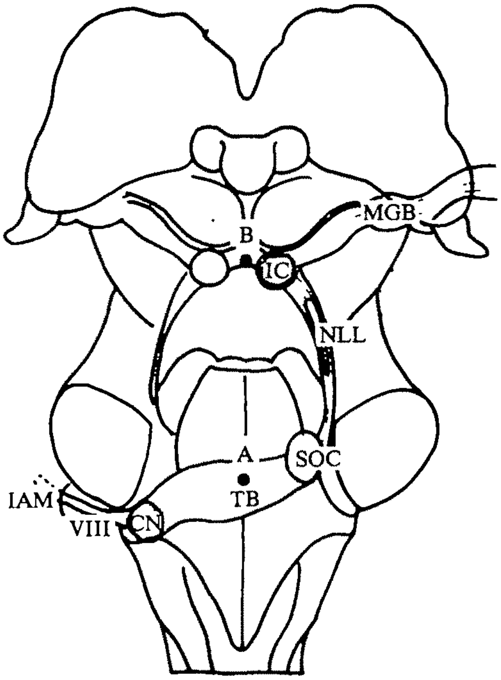

FIG. 3A, recording sites in the brain-stem. A = the midline of the dorsal pons at the level of the facial colliculus, B = the inferior colliculus. IAM = internal auditory meatus. CN = cochlear nucleus. TB = trapezoid body. SOC = superior olivary complex. NLL = nucleus of lateral lemniscus. IC = inferior colliculus. MGB = medial geniculate body.

positivity (P5) which was followed by an even higher amplitude negativity. On the other hand, preceding the P5 component, four distinct positive components (P1, P2, P3 and P4) were recorded from the pons. Their morphology remained similar at the inferior colliculus, only decreasing in size. Again, P5 was the only component that inverted its polarity between these two anatomical loci. There were no other locations where P5 inverted and these five positive components showed such a rapid increase or decrease in amplitude.

3. *Thalamus*

Evoked potentials were recorded from an electrode presumed to have been placed in the medial geniculate body during stereotaxic thalamotomy for the treatment of intractable pain. Our target was the ventrocaudal part of the centre median parafascicular complex. Polyphasic responses having a W-shaped configuration were recorded as the depth electrode was advanced into the presumed rostro-dorsal region of the medial geniculate. The potentials consisted of two

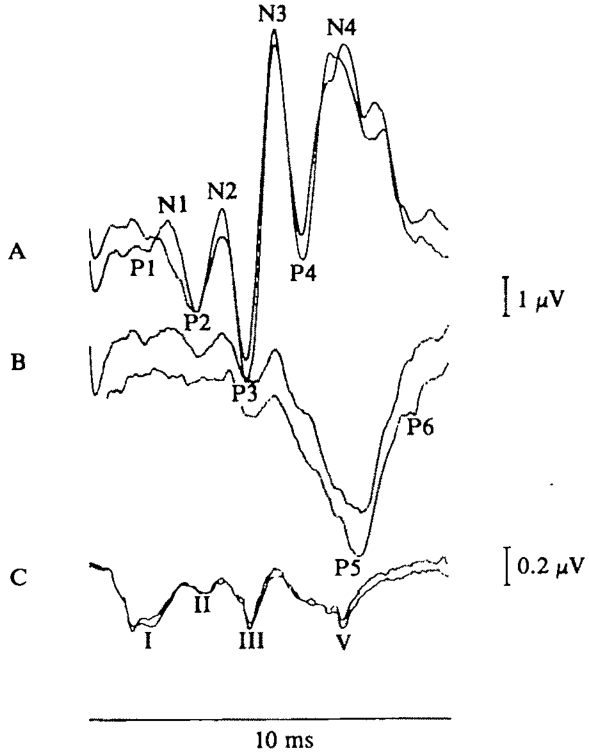

FIG. 3B, potentials evoked from the pons (A in fig. 3A) and midbrain (B in fig. 3A) by binaural stimulation. Three prominent positive components (P2, P3 and P4) from the pons (A) and a large P5 component from the inferior colliculus (B) predominate in the direct recordings. Note a rapid amplitude decline for P2, P3 and P4 components at the inferior colliculus (B). A relatively slow negativity after P4 at the pons (A) is a virtual mirror image of the P5 at the inferior colliculus (B). C = scalp (C3-A1) recordings.

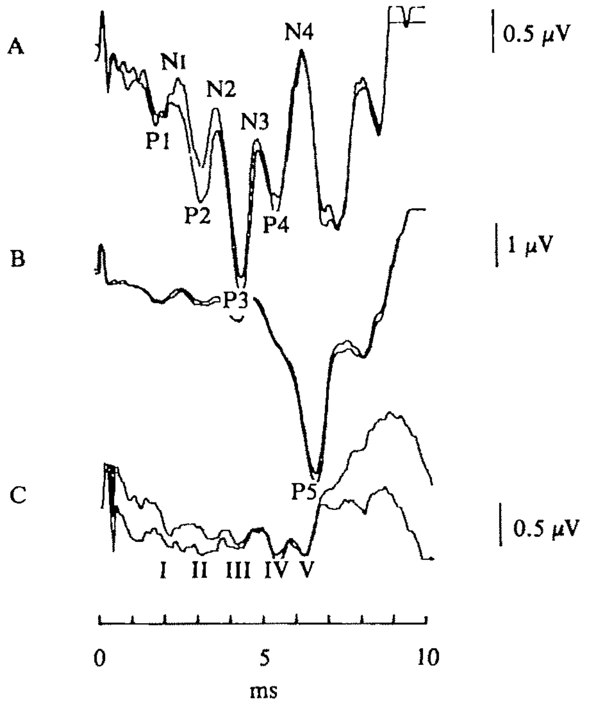

FIG. 3C, recordings from the same loci (A and B in fig. 3A) in another patient were essentially similar in the waveform although the relative size of the components slightly varied. Note high amplitude negativity following P5 component at the inferior colliculus (B). C = scalp (C3-A1) recordings.

distinct positive components corresponding to waves V and VI over the scalp (fig. 4). While the P5 component (the depth correlate of wave V) remained unchanged in amplitude as the electrode moved away from the rostro-dorsal part of the medial geniculate by 1 mm, the following P6 component was reduced to 62 per cent of that recorded at the medial geniculate. There was a similar differential amplitude reduction when the electrode was moved further away; while the P5 component was reduced to 74 per cent at a distance of 8 mm away from the medial geniculate, the P6 component was diminished to 16 per cent of its maximal amplitude at the geniculate. Bipolar recordings from the medial geniculate region with closely spaced electrodes (1 mm apart) also revealed a deflection synchronous with the P6 component obtained with the monopolar recordings.

Potentials from other regions in the thalamus were considerably attenuated, reflecting passive spread of the currents generated at distant sources. Recordings from electrodes aimed at the pulvinar, for instance, had a similar waveform as those from the mesencephalic central grey matter at the rostral end of the sylvian aqueduct, but their amplitudes were markedly diminished (fig. 5). Here again, the P6 component recordable at the mesencephalic central grey matter was profoundly attenuated at the pulvinar.

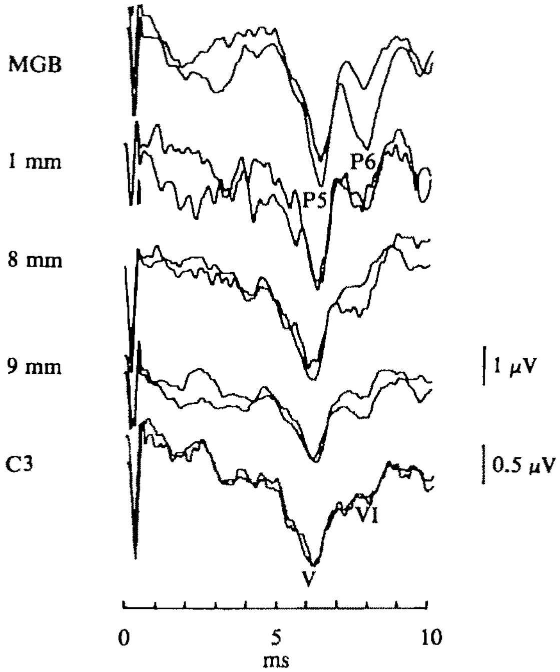

FIG. 4. Potentials evoked from the medial geniculate body (MGB) and adjacent thalamic nucleus (centre median parafascicular complex) to binaural stimulation. P5 and P6 components from the medial geniculate body which correspond to waves V and VI at the scalp, respectively, show a differential reduction in amplitude by the electrode displacement; a plot of P6 component reveals a more rapid decrement than P5.

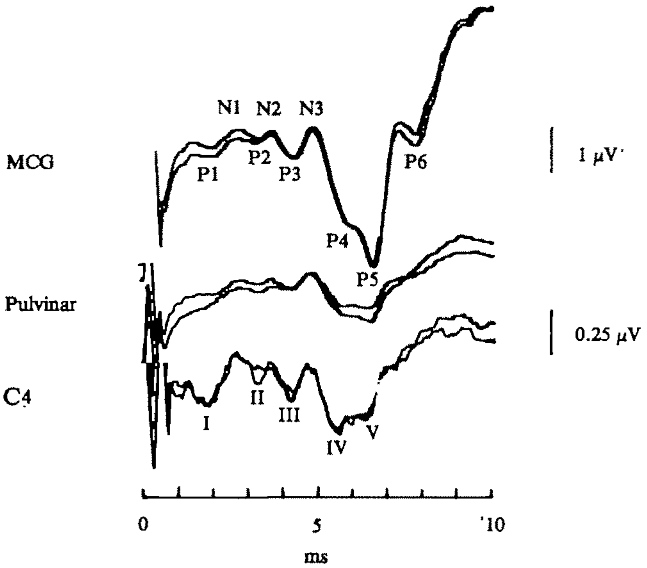

FIG. 5. Recordings from the pulvinar and mesencephalic central grey matter (MCG) at the rostral end of the sylvian aqueduct. Potentials evoked from the pulvinar are similar in morphology to those of the mesencephalic central grey matter but considerably diminished in amplitude, reflecting volume-conducted potentials from distant sources. C4 = scalp (C4) recordings with a reference to A2.

4. *Cortex*

Evoked potentials were recorded from the cortical surface of various parts of the brain. Although we have not examined systematically the potential distribution over the cortical surface, the potentials from the cortex displayed almost identical wave-forms and latencies as the recordings from the scalp. Only a small amplitude difference was present between the cortical and scalp recordings; the scalp potentials were reduced by approximately 10 to 20 per cent of the cortical potentials (fig. 6).

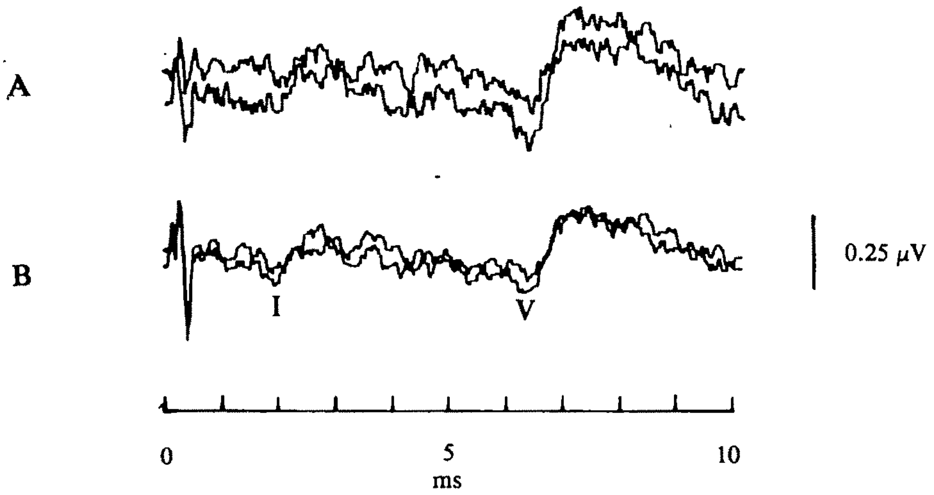

FIG. 6. Recordings from the frontal cortex to binaural stimulation. The morphology of the potentials from the cortex (A) and the scalp (B) is almost identical, only a minor amplitude difference is present. The scalp potentials are reduced by less than 20 per cent of the cortical potentials.

5. *Correlation between Intracranial and Scalp Potentials*

As shown in the previous recordings, it was our common experience that intracranial and scalp potentials were not always concurrent in peak latencies and often minor shifts were present between them. This raises the question of correspondence of a given intracranial potential to a scalp wave.

It was therefore necessary to take multiple recordings all the way from the brain-stem to the scalp to assess delicate changes in the waveform and latencies with a distance from potential sources. This was done with the use of our newly devised electrode described earlier. The initial recording site, indicated as 0 mm in fig. 7B, was in the IVth ventricle approximately 5 mm rostral to the level of the fastigium (fig. 7A). The aqueduct of Sylvius at the lower margin of the inferior colliculus was located 10 mm rostral to this site, and its rostral end, where it is continuous with the IIIrd ventricle, was about 25 mm from the initial electrode site.

In recordings from the IVth ventricle, 5 distinct positive components, separated by 4 negative components, could be identified within 8 ms after stimulation. Each component was designated by polarity and number in sequential order as in the previous recordings. Except for P1, peak latencies as well as amplitudes varied according to the locations of the depth electrode. The P2, P3 and P4 components were of maximum amplitude at the initial electrode site (0 mm) at which P4 had the largest amplitude. This component (P4) showed a most rapid decline, diminishing to one-third of its maximal amplitude at a distance of 2 mm and to one-seventh at 5 mm. By contrast, the P2 and P3 components were only reduced to three-quarters at a distance of 5 mm.

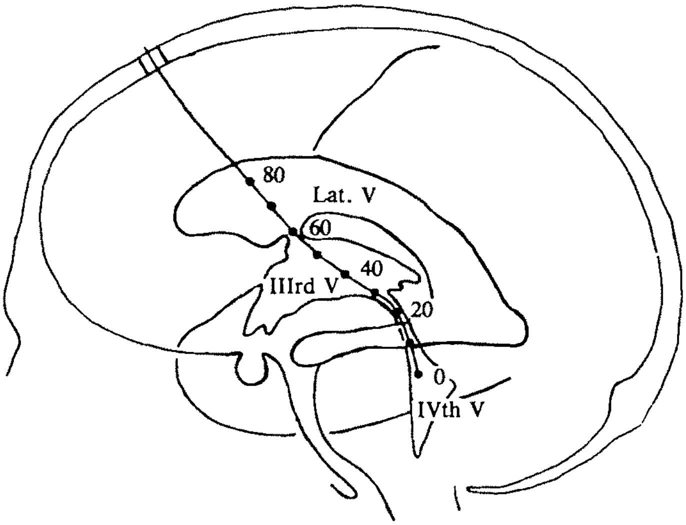

FIG. 7A, recording locations within the IVth, IIIrd and lateral ventricles (V). The initial electrode location within the IVth ventricle overlying the pons is indicated by 0 (mm). Double figures signify distances from the initial electrode location (0) in mm.

The P5 component had its maximum amplitude (5.41 μV) at the level of the inferior colliculus (12 mm), and fell off rapidly in both caudal and rostral directions. However, after passing through a presumed zero potential point, between the electrode locations at 5 mm and 7 mm, this component reversed its polarity and was increased in amplitude again to a maximum at the most caudal electrode location (0 mm). This inversion of the polarity of the P5 component is similar to those observed previously in figs. 3B and C.

Components P2 and P3 showed a steady decrease in latency as the electrode was moved away from the initial position to 5 to 7 mm rostral where the large P5 component began to appear. This decrease in latency was followed by an

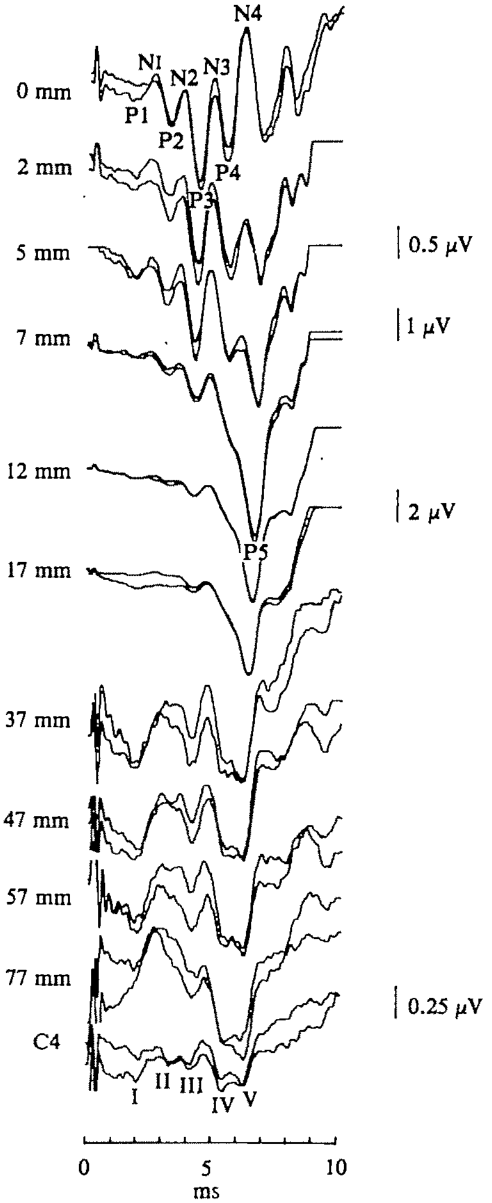

FIG. 7B, potentials evoked by binaural stimulation, recorded at the various levels along the electrode track. The figures in mm denote the actual recording sites measured from the 0 mm point. Note systematic changes in amplitudes and latencies of the intracranial-evoked potentials when the electrode is moved in the region of the brain-stem. The P2, P3 and P4 components are maximal at the pontine level whereas the P5 component is largest at the midbrain level. These potentials display rapid amplitude decrements within the brain-stem but only show slight changes beyond the midbrain to the surface.

increase due to the increasing effect of the predominant P5 component at the midbrain level. In contrast, the P4 component exhibited a systematic increase until it was merged in the large P5 component. These systematic changes in latencies observed within the brain-stem could be the result of interactions between potential fields generated by multiple sources, and small or no changes in latency were observed beyond the midbrain toward the scalp.

DISCUSSION

The human brain-stem auditory-evoked potentials recordable within 10 ms after click stimulation are characterized by a slow positive (peaking at 5 to 6 ms) and a negative (8 to 10 ms) potential. On these are superimposed 7 small positive wavelets. The earlier 5 components are superimposed on the falling phase and the later 2 components on the rising phase of the slow potential.

Our results provide further evidence of the sources of these fast and slow components recorded from the human scalp.

The responses from the cochlear nerve inside the internal auditory meatus consisted of a typical triphasic action potential followed by a small second negative potential. Wave I begins and ends on the same ordinate as its small initial positive (P1) component. Therefore, the peak of wave I occurs earlier than the following large negativity (N1). The morphology of the action potentials in man is quite similar to that of other mammals. In cat, Rupert, Moushegian and Galambos (1963) have recorded characteristic changes in the waveform and latency of the cochlear nerve action potentials as they moved the recording electrode overlying the cochlear nerve. They demonstrated that the two negative components recorded from the nerve outside the internal meatus are similar in waveform to N1 and N2 components of the round-window response, but their peak latencies are definitely longer than the round-window N1 and N2, respectively. However, when the electrode enters the meatus and passes beyond the glial margin the initial positive component disappears, and the first negative component decreases in latency and finally coincides in time with the round-window N1 at the most peripheral portion of the nerve. It has been well established in animals and man that wave I, recorded from the scalp with a reference to the mastoid or earlobe ipsilateral to stimulation, reflects the cochlear nerve action potentials which also give rise to the N1 component of the round-window response (Jewett, 1970; Lev and Sohmer, 1972).

By analogy with the animal studies, therefore, it can be concluded that wave I in man is generated, as in animals, mainly within a more limited portion of the distal cochlear nerve than has been generally expected in the previous literature (Starr and Hamilton, 1976), and the action potentials from a more proximal portion may contribute to a later wave but much less to wave I. As a corollary to this, N1 of the round-window response remains unchanged immediately after selective section of the VIIIth nerve in animals (Spoendlin and Baumgartner, 1977), and sometimes a normal wave I is obtainable in patients with a lesion of the VIIIth nerve itself (Selters and Brackmann, 1977).

The second negative (N2) component recorded within the internal auditory meatus has a peak latency in the range of wave II. The biphasic action potential recorded proximally also has a peak latency almost identical to the N2 component. Since the N2 component recorded distally has an earlier latency of onset than the action potential recorded proximally, this N2 component in man, and probably N2 at the round-window, cannot be a volume-conducted potential from the cochlear nucleus (Davis, Tasaki and Goldstein, 1952; Moushegian, Rupert and Galambos, 1962), and may represent repetitive firing of the first-order neurons (Tasaki, 1954).

The effect of stimulus repetition rate on the amplitude of the initial negative (N1) component from the cochlear nerve itself is consistent with previous human results: that increasing the repetition frequency from 10 to 60-70 Hz causes the amplitude of the N1 recorded at the round window (Eggermont and Odenthal, 1974), and that of wave I (Chiappa *et al.*, 1979), to decrease by approximately 45 to 55 per cent. These observations suggest that this decrease in amplitude with increasing repetition rate is the adaptation phenomenon which may occur at the synapses between the cochlear hair cells and the first-order neurons (Eggermont and Odenthal, 1974; Thornton and Coleman, 1975).

The conduction velocity of the human cochlear nerve is about 13 m. s^{-1} which is more than twice as fast as that of the guinea pig (5 to 6 m. s^{-1}: Davis *et al.*, 1952). This implies that the diameter of the fibres constituting the cochlear nerve varies in different species and thus should be taken into account in comparative studies of the brain-stem auditory-evoked potential in different species (Fernández, 1951).

Our results show clearly that wave II represents complex resultants of potentials generated in the VIIIth nerve as well as in the pons. A large positive potential (P2) concurrent with wave II is recorded from the midpons and this potential exhibits a rapid change in amplitude from the midpons to the midbrain. These observations in man are consonant with the results of animal studies which show that wave II is a composite of the activities of the VIIIth nerve, cochlear nucleus (Jewett, 1970; Lev and Sohmer, 1972; Buchwald and Huang, 1975) and trapezoid body (Achor and Starr, 1980*a*). The relative contribution of each of these generators to wave II, however, remains obscure.

The third positive (P3) component from the midpons, which starts and ends in time with wave III, also undergoes a rapid attenuation with a small displacement of the electrode within the brain-stem, but this component can be clearly traced from its maximum to the surface (fig. 7B). Jewett (1970), Lev and Sohmer (1972), and Buchwald and Huang (1975) have indicated the superior olivary complex as the primary generator for wave III in animals. Although we are unable to specify auditory nucleus or tract in the brain-stem which generates this component, our results suggest that wave III certainly originates from the pons.

Of all the pontine potentials, the fourth positive (P4) component, corresponding to wave IV, is the largest, and shows the most rapid decrement when the electrode is displaced; it is nearly merged in the following large potential (P5) at the midbrain. In addition, this component displays a systematic latency increase toward the midbrain, reflecting the increasing influence of the large midbrain potential.

In summary, the P2, P3 and P4 components are all maximal in amplitude at the pontine level, but they show differential reduction in amplitude by the same electrode displacements. This indicates that waves II, III and IV, which are the scalp correlates of P2, P3 and P4, originate from different sources within the pontine auditory structures. That the pontine region is responsible for the generation of wave IV is in conflict with the findings of Jewett (1970), and of Lev and Sohmer (1972), that the midbrain (inferior colliculus) is the most active site in the brain-stem at this timing; but is supported by Achor and Starr (1980*a*), who failed to obtain evoked activity in the inferior colliculus within this timing, and also by Buchwald and Huang (1975), who demonstrated the absence of any effect of colliculus lesions on wave IV.

In contrast to the earlier components, the intracranial potential corresponding to wave V (P5) is maximal at the midbrain. Moreover, this potential reverses its polarity between the pontine and midbrain regions. Mapping studies in man (Picton, Hillyard, Krausz and Galambos, 1974; Hashimoto, Ishiyama, Manaka, Ebe and Sano, 1981), and in animals (Allen and Starr, 1978), yielded a similar result: that wave V is maximal in amplitude over the frontal region and minimal over the occipital region. Interestingly, this distribution of potential over the scalp appears to reflect an almost vertically-orientated dipole set up in the brain-stem with a rostral-positive and caudal-negative potential field configuration. Lesion experiments by Buchwald and Huang (1975), and clinical studies in patients with midbrain lesions (Stockard and Rossiter, 1977; Hashimoto *et al.*, 1979), strongly suggest the inferior colliculus as the generator for wave V. Thus, we conclude, as did Lev and Sohmer (1972) and Buchwald and Huang (1975) in animals, that wave V originates from the colliculus.

Depth recordings from electrodes aimed at the medial geniculate revealed a positive potential (P6) following the large positive midbrain potential (P5). This potential, which is concurrent with wave VI, reaches its maximum amplitude within the medial geniculate and decays much more rapidly than P5 when the electrode is displaced. Bipolar recordings with closely spaced electrodes also demonstrate a potential synchronous with P6, thereby eliminating the possibility of its being a volume-conducted potential from other sources. Arezzo, Pickoff and Vaughan (1975) recorded auditory evoked potentials from the medial geniculate of a monkey, in which the earliest component is negative and has a peak latency of 7 ms. Although these potentials are opposite in polarity in man and monkey, they behave in a similar manner. Furthermore, the polarity difference could be a reflection of looking at the same source from the opposite side of the thalamic dipole, since our human recordings were made only from a limited portion of the medial geniculate. Clinically, Stockard and Rossiter (1977) described a selective abnormality of wave VI in a lesion of the medial geniculate. These complementary data, although limited in scope, do suggest that the geniculate is primarily responsible for the generation of wave VI.

Summarizing our results, the components of the brain-stem-evoked potentials, recorded from the scalp, have their origins in the VIIIth nerve and brain-stem; wave I from the distal portion of the VIIIth nerve; wave II from the VIIIth nerve and pons; waves III and IV from the pons; wave V from the midbrain (inferior colliculus); and wave VI from the thalamus (medial geniculate body).

In cat, Thurlow, Gross, Kemp and Lowy (1951) recorded from the inferior colliculus a slow positive wave, followed by a larger negative wave, as the most common type of response: the slow positive component had a peak latency of 3.0 to 4.5 ms from the start of the cochlear microphonic. This typical feline response resembles closely, in waveforms and latencies, the slow positive (peak latency of 5 to 6 ms) and negative (peak latency of 8 to 10 ms) components in man, in spite of slight differences in latencies due to the larger size of the human brain. In fact, this slow positive component in man was shown to be generated solely within the inferior colliculus.

Davis and Hirsh (1979) have called attention to the slow negative component (Davis SN10), whose rising phase follows the peak of the slow positivity. They speculated that this slow negativity represents the electrical output of dendrites and cell bodies in the grey matter of one or more of the brain-stem nuclei of the auditory system. We have good evidence to show, as had Thurlow *et al.* (1951) in animals, that this negativity reflects depolarization of dendrites and cell bodies within the inferior colliculus (unpublished data). However, since this negative component has a longer duration which is well outside the category of brain-stem auditory-evoked potentials, it seems appropriate to deal with the subject in a separate paper.

Finally, some points regarding the interpretation of the intracranial sources of the brain-stem auditory-evoked potentials and their conduction in volume to the surface must be clarified. Our findings show that the polarity of the maximal intracranial potentials concomitant with the surface-recorded components was positive and therefore of the same polarity as the surface components.

With regard to the source of potential in a volume conductor, Jewett (1970) and Lev and Sohmer (1972) claimed that a large amplitude, negative-going wave recorded with an intracranial electrode was evidence that it was generated at the electrode site. However, Achor and Starr (1980*a*) failed to find a consistent relationship between the polarity of the maximum potentials in the brain-stem and that of the surface components. Be that as it may, the consistent positive polarity in our intracranial recordings may be related to the electrode locations which are rostral and dorsal to the pontine generators and thus, the electrode sees only the wave front of the ascending depolarization (Woodbury, 1965) along the brain-stem auditory pathway.

By tracing these potentials from the brain-stem to the surface, two important aspects of volume conduction are made clear. First, intracranially-recorded components of the brain-stem auditory-evoked potentials undergo very rapid changes in amplitude within the brain-stem but only slight changes in the more rostral regions. Thus, while the amplitude gradients are steep within the brain-stem (although different to some degree in each component), they become similarly more shallow with increasing distance from the active sources, as has been demonstrated for the early somatosensory-evoked potentials in animals (Arezzo, Legatt and Vaughan, 1979). Secondly, due to an overlap of separate potentials, the intracranial components show minor but systematic shifts in latency with distance from the sources. This effect must be kept in mind when one is thinking of interpreting a 'concurrent' intracranial potential as the source of a surface-recorded potential.

SUMMARY

Brain-stem auditory-evoked potentials were recorded in neurosurgical patients from surface electrodes applied to the VIIIth nerve, medulla, pons, midbrain and cortex; from depth electrodes in the thalamus; and from a movable electrode in the IVth, IIIrd, and lateral ventricles. The potentials recordable over the scalp within 10 ms after click stimulation are characterized by a slow positive wave (peaking at 5 to 6 ms) and a negative wave (8 to 10 ms) with 7 small positive wavelets superimposed upon them. The sources of these components have been identified by observing their increased amplitude in depth recordings, and by tracing the potentials from their intracranial maxima to the scalp. Wave I is generated within the most distal portion of the VIII nerve; Wave II in the proximal part of the VIIIth nerve and pons; Waves III and IV in the pons; Wave V in the midbrain (inferior colliculus); and Wave VI the medial geniculate body. Both slow positive and negative components have their origins in the inferior colliculus. Intracranially-recorded brain-stem auditory-evoked potential showed very rapid changes in amplitude within the brain-stem but only slight changes in the more rostral regions, although their amplitude gradients varied in the different components. They also demonstrated minor but systematic shifts in latency with distance from the potential sources, reflecting a significant overlap of separate potentials. This effect must be taken into account in the interpretation of a 'concurrent' intracranial potential as the source of a far-field surface-recorded potential.

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(*Received April 1, 1981*)

Brain (1981), **104**, 861–872

DISSOCIATION OF SPATIAL INFORMATION FOR STIMULUS LOCALIZATION AND THE CONTROL OF ATTENTION

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BEHAVIOUR following complete midline section of the corpus callosum in humans, a surgical procedure preformed for the control of epilepsy, reveals intact sensory capacities within each visual half-field, but an inability to perform explicit interfield comparisons of stimuli presented on both sides of the visual midline (Gazzaniga, 1970; Gazzaniga and LeDoux, 1978). This occurs because the geniculo-striate sensory projections to areas 17 and 18 of visual cortex are almost exclusively representative of the contralateral visual half-field: ipsilateral representation is provided only indirectly through interconnections between the hemispheres *via* the corpus callosum (Choudhury, Whitteridge and Wilson, 1965; Berlucchi, Gazzaniga and Rizolatti, 1967; Hubel and Wiesel, 1967; Rocha-Miranda, Bender, Gross and Mishkin, 1975). Loss of ipsilateral sensory representation in the isolated cerebral hemisphere following callosal section is not unique to the visual modality; analogous findings have been noted as well with regard to auditory (Springer, Sidtis, Wilson and Gazzaniga, 1978) and tactile stimulation (Gazzaniga, Bogen and Sperry, 1963).

Despite these severe sensory disconnections, corresponding disruptions of visual-motor behaviour are less evident. Commissurotomy patients direct action within the environment with little overt difficulty or hesitation: they are able to walk, run, avoid obstacles, and, in one instance, operate a motorcycle. While much of the co-ordination of such behaviour is subcortical (Grillner, 1975; Shik and Orlovski, 1976), the selection of specific goals for directed behaviour depends on internal representations and therefore, presumably, requires cortical involvement. If the separated hemispheres vied for the control of behaviour, one would anticipate an organism in a state of constant response competition. On the other hand, control of behaviour by a dominant hemisphere would predict a state of unilateral neglect. While either state can be elicited in the laboratory, neither is the rule in the normal environment. To explain the integrity of co-ordinated visual-motor behaviour, it was suggested that, although visual information is not transferred between areas subserving explicit stimulus identification, integration may occur across the visual midline for the control of selective visual attention. By providing the commissurotomy patient with bilateral visual information for the selection of specific goals, such integration could account for the absence of both unilateral neglect and constant competition between the hemispheres for the control of directed behaviour.

The two studies reported below provided evidence that following callosal surgery, a bilateral representation of the visual world is available for the allocation of attentional capacities, and that a distinction can be made between spatial information as it is used for the control of attention and that used for explicit stimulus localization.

Experiment 1. Intra and Interfield Manipulation of Attention

The paradigm employed to manipulate visual attention and measure its spatial locus was analogous to one originally proposed by Posner and his colleagues (Shulman, Remmington and McClean, 1979; Posner, Snyder and Davidson, 1980; Posner, 1980). These authors noted that response latencies are reduced when an antecedent cue indicates a target's subsequent spatial location, thereby allowing observers to direct attention to the appropriate location prior to the onset of the target. Such spatial priming was shown to occur both when the cue and target appear in the same region and when the target's location has to be inferred based on a cue which appears elsewhere.

It was determined here that spatial cues effectively reduce response latencies in the commissurotomy patient, even when they require access to visual information from both visual half-fields.

Subjects. Two commissurotomy patients, P.S. and J.W., volunteered to serve as observers in these experiments. Both had undergone complete midline section of the corpus callosum with anterior commissure left intact. Formal testing of J.W. after callosal section revealed that he could accurately name stimuli presented to the right of central fixation, but was unable to name any stimuli presented at least 1 deg of visual angle to the left of fixation. In general, similar results have been obtained for P.S. However, this patient has an extensive right hemisphere language capacity (Gazzaniga, Volpe, Smylie, Wilson and LeDoux, 1979), and has recently demonstrated interhemispheric transfer of linguistic information. Such transfer appears to be limited to phonetically codable information, and does not represent visual transfer (Gazzaniga, Sidtis, Volpe, Smylie, Holtzman and Wilson, 1982.) Additional patient information is provided elsewhere (Wilson, Reeves and Gazzaniga, 1978; Sidtis, Volpe, Holtzman, Wilson and Gazzaniga, 1981).

Method. During an experimental session, the observer, seated 0.5 m from a video monitor, viewed stimuli generated and controlled by an Apple II micro-processor. Viewing was binocular and under daylight illumination. Two manual response keys were situated in front of the observer and connected to a digital timer, which allowed for the computation of response latencies.

The spatial framework for the experiment, which appeared at all times for all conditions, was provided by a computer-generated background visual display consisting of two 3 × 3 cell grids located 4 deg on either side of a central fixation spot and symmetrical about the horizontal and vertical meridians (fig. 1). On all trials, one of eight equally probable target digits appeared for 150 ms in one of the cells, and the observer's task was to indicate, by pressing the appropriate key, whether the target digit was even or odd.

The observer was told that on most trials, prior to the onset of the target, a cue would appear indicating the target's subsequent spatial position. On 59 per cent of the trials in the Within-field Condition, 1.5 s before the onset of the target, an 'X' did, in fact, appear for 150 ms in the cell corresponding to the target's spatial position (valid cue); on 12 per cent of the trials, however, the target and the cue appeared in the same grid, but within *different* cells (invalid cue); and on the remaining 29 per cent of the trials the 'X' appeared superimposed on the central fixation stimulus (neutral cue). Since both the target and cue appeared in the same visual half-field on valid and invalid trials, any benefit or cost derived from the spatial cues did not require the integration of sensory information across the visual midline.

This was not the case for the blocks of trials in the Between-field Condition. The valid spatial cue on these trials did not specify the actual location of the target but appeared, instead, in the homologous cell within the opposite grid. Analogously, the invalid cue appeared in a different relative position in the opposite grid. Thus, for between-field trials any benefit or cost derived from the spatial cues required access to visual information from both visual half-fields. In all other respects, between-field and within-field trials were identical.

Since it has been shown that the detectability of a visual stimulus can be enhanced when an antecedent visual stimulus is presented in a mirror-symmetric region of the opposite hemifield (Singer, Zihl and Pöppel, 1977), homologous rather than mirror-symmetric locations were chosen for the valid cue trials in the Between-field Condition. Likewise, we did not include invalid trials in which mirror-symmetric locations were stimulated. Thus, the efficacy of the spatial cue on between-field trials in the present paradigm required voluntary control over the locus of visual attention.

Prior to each block of trials, the observer was told whether the within-field or between-field contingency applied, and was instructed to maintain fixation of the central spot at all times. Both P.S and J.W. are highly trained at maintaining central fixation for lateralized stimulus presentation. In order to verify that trials in which central fixation was disrupted occurred infrequently, a video camera equipped with a 10:1 zoom lens recorded the observer's eye movements throughout the experiment.

Each block of trials contained a random permutation of the representative valid, neutral, and invalid trials, with an equal number of replications in each visual half-field. Blocks of trials were presented in a counterbalanced order, and hand use was alternated between blocks.

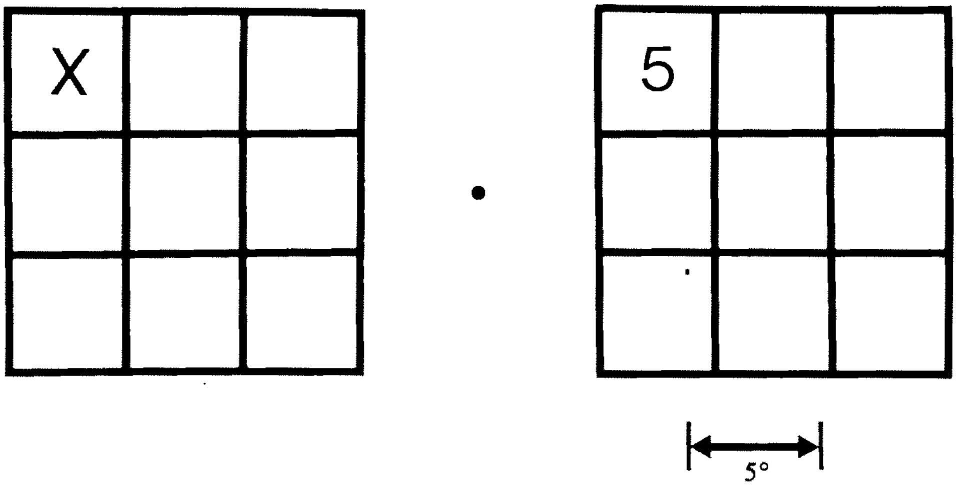

FIG. 1. Example of background visual display and stimuli for a valid cue trial in the Between-field Condition. For the initial portion of each trial, two empty grids were displayed on either side of the central fixation dot. Next, the spatial cue ('X') appeared for 150 ms in one of the grid cells. Following a 1.5 s interval, during which only the empty grids were displayed, the target digit was presented for 150 ms in the opposite grid, in the same relative position as the cue. Each square cell within a grid subtended 4 deg of visual angle, and all digits and letters, which appeared centred in these cells on experimental trials, subtended 1 × 2 deg of visual angle (for description of the remaining conditions, *see text*).

Results and Discussion

Response latencies on a total of 272 trials, 8 blocks of 34 trials, were collected from each observer. Approximately 7 per cent of these were excluded from the analysis because the observer responded incorrectly. An additional 4 per cent were considered 'missed' because a response did not occur within a reasonable period of time (2.0 s for P.S.; 2.5 s for J.W.), and these trials were also omitted from the analysis. Visual analysis of the video records indicated that, in fact, trials in which observers moved their eyes from central fixation to a position within a grid were very infrequent. Thus, no steps were taken to exclude these trials from the analysis. Incorrect and 'missed' trials did not vary systematically as function of condition nor did their exclusion alter the general pattern of the results for either observer.

The mean response latencies for the analysed trials, averaged across observer, visual half-field, and response hand, are summarized graphically in fig. 2. The three spatial cue types are indicated along the abscissa, and the ordinate represents the mean response latency associated with each type of trial. The data are presented separately for the Within-field Condition (filled squares) and the Between-field Condition (empty squares).

The results here are quite clearcut: response latency is reduced when the observer has prior information regarding the target's spatial location. The most striking aspect of these data is the similarity of the observers' performance under the two conditions, indicating that the spatial cue is effective both when it appears in the same visual half-field as the target and when it appears in the contralateral half-field.

Of particular interest is the detrimental effect on response latency of the invalid cue in the Between-field Condition, which implies that, when attention is directed across the midline, it is specific to the target's location and not simply directed in general to the contralateral visual half-field. If the latter alternative were the case, response latencies on valid cue trials would not be expected to differ from those on invalid cue trials. The results obtained here are quite to the contrary: performance on these two types of trials shows contrasting effects relative to the neutral cue trials.

The trends described above were supported statistically by a 3-way ANOVA (Observer X Condition X Cue Type) which revealed a highly significant main effect of cue type ($P < 0.001$). In addition, the main effect of observer ($P < 0.001$), and the interaction between observer and cue type ($P < 0.005$) were also significant. The remaining main effect and two-way and three-way interactions were not significant. The significant difference between observers was due to shorter response latencies, overall, of observer P.S. P.S. also showed a smaller range of response latencies as a function of cue type, accounting for the significant interaction that was obtained. It should be stressed, however, that, despite the significant interaction between observer and cue type, the relative effects of the three spatial cue types on response latencies were the same for both subjects.

The observed ability of commissurotomy patients to integrate the visual half-fields for the control of attention is in dramatic contrast to their inability to perform explicit interfield visual comparisons. It can be inferred that interfield comparisons depend primarily on visual cortex, since they are typically disrupted when posterior callosal section or damage disconnects visual cortex (Maspes, 1948; Gazzaniga and Freedman, 1973; Sugishita, Iwata, Toyokura, Yoshioka and Yamada, 1978; Levine and Calvanio, 1980; Sidtis *et al.*, 1981), but not when the lesion is restricted to the anterior callosum, in which case occipital interconnections are spared (Sweet, 1941; Geschwind and Kaplan, 1962; Gordon, Bogen and Sperry, 1971; Gazzaniga, Risse, Springer, Clark and Wilson, 1975). The present data imply that, in contrast, visual information for the control of attention projects to brain structures that maintain functional bilateral visual representation following callosal section. Thus, in the present paradigm, it was predicted that bilateral visual information would not be available for explicit stimulus localization.

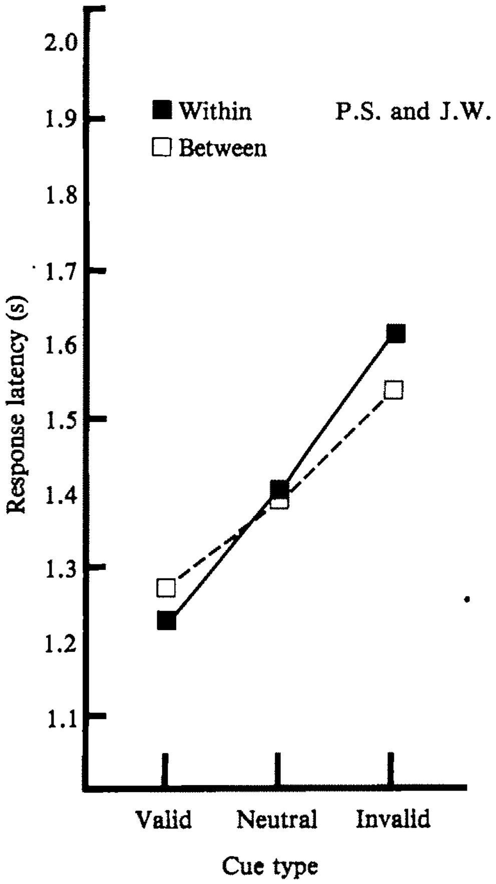

FIG. 2. Response latency as a function of spatial cue type. Data are presented separately for the Within-field Condition and the Between-field Condition. Each data point represents the average of two observers, with each given equal weight.

Experiment 2. Intra and Interfield Spatial Localization

In order to assess the availability of visual information for explicit interfield comparisons, the same background configuration and temporal parameters were used to collect additional data in which an explicit comparison of two spatial positions was required. If the visual half-fields, which were previously integrated for the control of attention, proved to be disconnected for explicit stimulus localization, performance under within-field conditions would be expected to differ from performance under between-field conditions.

As in Experiment 1, fixation of the central spot was required throughout each trial. In the Within-field Condition, an 'X' appeared in one of the grid cells for 150 ms, followed 1.5 s later by another 150 ms presentation of an 'X', either within the same cell or in a different cell. In the Between-field Condition, the two 'X's appeared in homologous or different cells on different grids. The observer was instructed to respond 'same', by pressing the appropriate key, when the stimuli fell in the same or homologous cells, and, otherwise, to respond 'different'. The relative frequency of 'same' and 'different' trials in both conditions was 50 per cent.

Results and Discussion

A total of 144 trials—2 blocks of 36 trials for each condition, alternated between hands and presented in a counterbalanced order—were collected from each of our observers, P.S. and J.W. An equal number of replications in each visual half-field were contained within each block of trials.

Observers' performance on the same/different task, expressed in terms of percentage correct, differed dramatically for our two conditions. In the Within-field Condition, P.S. and J.W. were accurate in their judgements on 83 and 93 per cent of the trials, respectively. This is comparable to their over-all performance on the odd/even judgements in our first experiment. In the Betweeen-field Condition, however, performance fell to 64 correct and 56 per cent correct, respectively. Unlike the spatial priming effect obtained in Experiment 1, the difference between within-field performance and between-field performance on the same/different task was highly significant for each observer ($P < 0.001$). This finding contrasts with that obtained for normal observers who have little difficulty with this task, and for whom the accuracy for both within-field and between-field trials is near-perfect.

Although observer P.S. was significantly impaired at between-field comparisons, it was somewhat surprising that his between-field performance was slightly better than chance ($P < 0.05$). The reason for this is not clear. The recent evolution of interhemispheric transfer of phonetically-encodable stimulus information in this patient (Gazzaniga *et al.*, 1982) may have provided a basis for transfer in the present context. However, since, overall, P.S. was frequently incorrect in his judgements in the Between-field Condition, the occurrence of such transfer would be clearly insufficient to account for the similarity of within-field and between-field performance observed in the priming task.

J.W., on the other hand, is unable to transfer visual information of any kind for overt naming, and this observation is consistent with the finding that his performance at the interfield comparison task did not depart significantly from chance.

The Resolution of Spatial Information for Attentional Control and Stimulus Localization

The results of our two experiments imply that the commissurotomy patient has access to bilateral visual information that can be used to specify the locus of visual attention, but that is unavailable for explicit interfield visual comparisons. The following analyses were performed to examine the spatial resolution of visual information for attentional control, and to contrast the specificity of such information with that available for explicit interfield comparisons.

As noted above, the contrasting effects of the valid and invalid spatial cues in the priming task indicate that, when attention was directed across the visual midline, it was specific to the region of the cued target location. This finding implies that the effective locus of attention had a greater degree of specificity than the over-all size of the 3 x 3 cell matrix within which the target appeared. It remains possible, however, that interfield spatial priming occurred both within the cued cell, as well as within cells which were nearby the cued target location. If so, response latencies on invalid cue trials would be expected to decrease as the relative proximity of the cued and actual target location increased. In order to explore this possibility, response latencies on invalid cue trials in which the target appeared in a cell adjacent to the cued cell were compared with those in which the cue and target appeared in relatively non-adjacent cells. Adjacent cells were defined as those abutting or immediately diagonal to the cued cell.

The results of these computations for both observers indicate that the priming effects in the Between-field Condition did not generalize to cells adjacent to the cued cell. For invalid cue trials in which the target appeared in a cell adjacent to the cued location, the mean response latencies for P.S. and J.W. were 1.45 s (N = 7; SE = 0.14 s) and 1.64 s (N = 7; SE = 0.20 s), respectively. These values contrast with average response latencies on valid cue trials for P.S. and J.W. of 1.29 s (N = 70; SE = 0.03 s) and 1.26 s (N = 67; SE = 0.04 s), respectively.

In addition, the average performance of our two observers was similar for targets appearing in cells adjacent and non-adjacent to the cued cell (average response latencies = 1.54 s and 1.50 s, respectively). When each observer is examined separately, however, the individual means for non-adjacent invalid trials are somewhat problematical. The average response latency on these trials for observer J.W. was 1.72 s (N = 7; SE = 0.21 s). This value is comparable to J.W.'s performance on adjacent invalid cue trials. On the other hand, the average response latency for P.S. on non-adjacent invalid cue trials, was 1.29 s (N = 7; SE = 0.12), which is identical to his performance on interfield valid cue trials. This finding, that response latencies decreased with increasing spatial disparity between the cued and actual target location, is opposite to what would be expected if the locus of priming generalized to neighbouring cells in the Between-field Condition. Rather, it may simply be a consequence of some combination of random variation, the relatively small samples which were available for these comparisons, and the smaller priming effects, overall, for observer P.S. In sum, then, the above computations imply that the locus of attention in the Between-field Condition was specific to the cued cell.

Analysis of the results of Experiment 2, on the other hand, implies that, at least for observer J.W., bilateral spatial information was unavailable for explicit interfield comparisons, even in a crude form. An argument analogous to the one made above regarding the spatial priming effects that were obtained in Experiment 1 can also be made for the results of Experiment 2: if spatial information from both hemifields was available for the interfield comparison task, observers should have been most likely to erroneously equate the positions of stimuli which appeared in relatively adjacent cells. Stimuli appearing in relatively non-adjacent cells, which represented a spatial separation of at least 9 deg of visual angle, should have been easily distinguishable as appearing in different locations.

The results for observer J.W. indicate that this was not the case. The finding that his performance at the same/different task was not superior to chance is, of course, inconsistent with this interpretation. In addition, a comparison of J.W.'s performance on 'different' trials in which adjacent and non-adjacent cells were represented indicates that the relative proximity of the two 'X's did not systematically affect his performance. Thus, J.W. erroneously responded 'same' on 33 per cent (4/12) of the 'different' trials in which adjacent locations were represented; while he erroneously responded 'same' on 54 per cent (13/24) of those in which non-adjacent cells were represented. The difference between these values is non-significant ($\chi^2 < 1$), and the tendency for adjacent locations to be less confused than non-adjacent ones is contrary to what would occur if crude bilateral spatial information was available for interfield comparisons.

As noted above, the performance of observer P.S. at the same/different task was superior to chance. In addition, despite having been informed that 'same' and 'different' trials were equiprobable, P.S. had a strong bias to respond 'different' in the Between-field Condition. Thus, while he was correct on only 44 per cent (16/36) of the 'same' trials in the Between-field Condition, he was correct on 83 per cent (30/36) of the 'different' trials. On 'different' trials, P.S. was incorrect on 33 per cent (4/12) of the trials in which relatively adjacent cells were represented and on only 8 per cent (2/24) of those in which non-adjacent cells were represented. The difference between these values is not significant ($\chi^2 = 3.6$; $P > 0.05$), but the trend is in the direction predicted if confusions between adjacent cells did occur. Thus, paracallosal interhemispheric transfer of a crude form of spatial information may have facilitated interfield comparisons for P.S. It is important to note that, whereas P.S. may have confused adjacent cells for explicit interfield comparisons, the effective locus of attention in the priming task appeared to be specific to the cued target location.

In sum, the over-all results of the above computations imply that the resolution of bilateral spatial information for the control of the locus of visual attention is superior to that available for explicit stimulus identification. It should be stressed, however, that the dimension of the individual cells used in the present studies was quite large (4.5 deg of visual angle). It remains to be determined whether differences between within-field and between-field performance would emerge when finer spatial discriminations are required.

GENERAL DISCUSSION

The results of these experiments imply that stimulus information as it exists for the explicit identification of spatial location can be distinguished from that used to direct the locus of visual attention. Several researchers have proposed that these functions are subserved by different anatomical pathways (Ingle, 1967; Trevarthen, 1968; Schneider, 1969). While their positions differ in detail, in general, it has been suggested that the primary geniculo-striate visual pathway plays a dominant role in the identification of visual stimulation, while the secondary colliculus-pulvinar-parietal visual pathway is concerned primarily with the allocation of visual attention.

To date, supportive evidence for the existence of two functionally and anatomically distinguishable visual systems in humans has derived exclusively from observations of residual function following lesion of a critical brain structure. It has been noted, for example, that, while damage to primary visual cortex results in visual field deficits (for instance, an inability to identify stimuli within the area of the scotoma), the patient is still capable of pointing to and foveating stimuli within the blind field (Weiskrantz, Warrington, Sanders and Marshall, 1974; Perenin and Jeannerod, 1975). On the other hand, studies of patients with damage to parietal cortex, and more recently the superior colliculus and pulvinar, reveal individuals with intact sensory capacities but a constellation of attentional deficits in response to contralateral stimulation (Heywood and Ratcliff, 1975; Friedland and Weinstein, 1977; Zihl and Von Cramon, 1979). Whereas these observations have demonstrated that one visual function can be spared when the other is lost, the co-existence of two visual systems simultaneously subserving different visual functions has heretofore been unreported.

In addition, the assessment of attentional capacities in patients with parietal or occipital damage has typically focused on overt motor behaviours associated with changes in the locus of attention (for example, the presence or absence of elicited saccadic eye movements; reaching or pointing movements of the hand) rather than on attentional control *per se*. While visually-elicited motor behaviour depends on an observer's capacity to orient to visual stimulation, the absence of such behaviour does not necessarily imply a deficit in the antecedent attentional processes (Robinson, Goldberg and Stanton, 1978).

The present findings provide the first demonstration of two functional visual systems in patients with intact, albeit interhemispherically disconnected, parietal and occipital cortex, under conditions in which performance depended upon the observer's ability to direct attention within the sensory environment independent of the capacity to execute specific motor acts. If the observed spatial priming effects reflect predominantly parietal involvement, as the existing clinical literature would suggest, the question then arises as to the source of ipsilateral visual representation in parietal cortex. Two possibilities exist in this regard: following callosal section, ipsilateral visual representation may be provided directly *via* collicular-cortical projections, or it may be provided indirectly *via* the intact anterior commissure. Neither potential source of ipsilateral representation can be ruled out at the present time.

These data also raise questions concerning the cortical lateralization of attentional control. The present data imply that each separated hemisphere is provided with bilateral visual representation for the allocation of attentional resources. It remains to be determined whether, following callosal section, the disconnected hemispheres subsequently work in phase in the control of attention, or whether attention is controlled by a dominant hemisphere.

SUMMARY

Following complete midline section of the corpus callosum, each separated hemisphere is unable to explicitly localize visual information appearing in the ipsilateral visual half-field and thus projecting to the other half-brain. Two studies are reported which reveal that, while commissurotomy patients are impaired at explicit interfield comparisons, the attentional system has access to both visual half-fields, thereby allowing one hemisphere to direct attention to specific spatial loci in the ipsilateral visual half-field.

ACKNOWLEDGEMENTS

Aided by USPHS grant No. 2 RO1 NS 15053-02, the Alfred P. Sloan Foundation and the McKnight Foundation. We are grateful to Drs H. A. Sedgwick, A. Arditi and L. Festinger for their critical comments on an earlier version of this manuscript.

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(*Received December 16, 1980*)

Brain (1981), **104**, 873–876

NOTICES OF RECENT PUBLICATIONS

Essays in Neurochemistry and Neuropharmacology. Volume 5. Edited by M. B. H. Youdim, W. Lovenberg, D. F. Sharman and J. R. Lagnado. Chichester: John Wiley. Pp. 153. Price £16·50.

This latest volume of Essays contains some high-powered biochemistry, but the biological aspect is the focal point in most of the essays.

In Chapter 1 the relations between depolarization, ion concentration, carrier systems, binding and biosynthesis are explored for tyrosine and tryptophan. Three stereospecific transport systems are stipulated, even for the transport across synaptosomal membranes, each depending on different factors for optimal activity.

The next article discusses the basis of the nocturnal rise in N-acetyltransferase observed in the pineal gland of the rat. Its induction *in vitro* is only possible in pineal tissue, and the enzymes and nucleotides determining this induction form the main topic of the article. It is a unique system, in that photic input controls the activity of noradrenergic β-receptors which in turn is responsible for RNA synthesis.

Chapter 3 discusses the importance of octopamine in vertebrate and invertebrate organisms and the author remains somewhat doubtful about the role of this amine in the physiology of vertebrates. However, there are several examples of excess of octopamine in human disease, and this fact means that one has to take the study of octopamine seriously.

Dopamine release from amacrine cells of the retina by light makes the eye an ideal tool for the study of the relation between dopamine release and synthesis, and thus of the biochemistry of the effect of light on tyrosine hydroxylase (Chapter 4). The next article is a discussion of similarities and differences between the action of amphetamine on animals and man, and therefore of the validity of observations on animals in the assessment of human responses. Perseveration is perhaps the main abnormality observed in all species. The last chapter introduces the relatively new term of 'suicide inhibitors of enzymes'. Such inhibitors bind to the active site of an enzyme, where they are transformed by the enzymic activity into a reactive compound which becomes an irreversible inactivator of the enzyme itself. Since several inhibitors of monoamine ozidase and of GABA transaminase belong to the suicide inhibitors, this subject is of great importance to the pharmacologist.

M. VOGT

Kuru: Early Letters and Field-Notes from the Collection of D. Carleton Gajdusek. Edited by Judith Farquhar and D. Carleton Gajdusek. 1980. Pp. 366. New York: Raven Press. Price $43.52.

How can one describe this fascinating book—essential scientific reading, an adventure story, a sophisticated epidemiological study, or a fairy tale? A bit of all four I would say. Even for someone like myself who thought that he was already fairly well informed about the story of the discovery of kuru, this book adds an entirely new dimension. No doubt this is because the main part of the book is composed of letters that were written in the course of that vital early period 26 December, 1956 to 28 January, 1958. As Gajdusek says in the introduction, they 'allow the reader to trace the diverse origins and meandering paths of ideas, recording something of the personality conflicts and compatibilities and the varied and diverse devotions that led to the discovery and first investigation of kuru'. The letters are certainly so frank that one does not even need to read between the lines, and Gajdusek does not appear in any way to have suppressed anything that is uncomplimentary to him. This is not really surprising since most people who know him are agreed that he has a fairly thick skin!

It is perhaps a pity that the preface, editorial note and introduction are so long since they rather tell the reader what he is going to read, and I think that much of this could, with advantage, have been deferred until after the letters. But suddenly one is presented with the letter written by Zigas to Gunther (it is also a pity that the reader is not reminded more often about who the writers were, since I had continually to refer to the list of correspondents hidden at the back of the book) to the effect that he had identified among the Fore people what was probably a new form of encephalitis attributed by the local inhabitants to sorcery and called 'kuru'. Zigas, who was medical officer in the Territory of Papua and New Guinea Public Health Department stationed at Kainantu in the Eastern Highlands, then summarized the clinical features of no less than 27 cases and suggested to Gunther, who was at that time assistant administrator in the Territory, that kuru was clearly worth further close investigation. Prophetic words! Zigas' name appears on innumerable occasions in the correspondence and Gajdusek is unstinting in his praise of what Zigas contributed.

The Australians were clearly at that time on the point of participating in an epidemiological study with the principal aim of identifying the causal virus but while they were discussing the potential dangers from hostile native reaction, Carleton Gajdusek arrived in Port Moresby fresh from a period of study under Sir Macfarlane Burnet in the Walter and Eliza Hall Institute of Medical Research in Melbourne. At that time Gajdusek was on a short visit to plan out sites for a potential child study. There, however, he received first-hand information about kuru and within two days of his arrival he was already writing about the importance of comprehensive microbiological and neuropathological studies and asking for detailed information as to how brains should be removed and fixed! The Australians did not appreciate Gajdusek's intervention. Within two weeks of his arrival he received one rather pointed letter asking him when he would be leaving New Guinea and what future plans he had for epidemiological or child studies in the region. But within three weeks of his arrival in New Guinea, Gajdusek had identified 41 cases of kuru, had a functioning kuru hospital with 25 patients, and had undertaken 30 lumbar punctures. He had also mastered the Fore language and had developed a fairly accurate technique for taking case and family histories. One rather fortunate feature about the study was that Gajdusek found the natives, although living in stone age settlements, to be 'as accurate and good informants and observers as any parents I ever encountered in civilised pediatric practice'. They certainly seemed remarkably receptive to the investigations required of modern medicine. Gajdusek was already 'placing his bets' on some form of heredo-familial degenerative disorder in view of the family histories he had already elicited, and in view of the absence of any acute encephalitic-like illness. He was clearly there to stay, and the Australians decided to withdraw but they did offer to help in any way possible with laboratory studies, and in all fairness to Gajdusek, he did in the earlier stages of the study send as much material as he could to the Australians. His arrival on the scene is described as an extraordinary intrusion by an extraordinary individual with an intelligence quotient up in the 180s and the emotional immaturity of a 15 year old! Perhaps it is fortunate that he is so thick-skinned. Later in the correspondence it is, however, clearly accepted that Gajdusek was the best man possible for the job he had undertaken.

Perhaps I have gone into too much detail in these introductory paragraphs but they do, I hope, set the scene. Thereafter the clinical and epidemiological studies continued and within two months Gajdusek had come to the conclusion that about 1 per cent of the population was afflicted by this incurable disease. Innumerable specimens of all natures were sent off to various laboratories throughout the world and various treatments tried without success. The accomplishments and frustrations, however, can really only be appreciated by reading the letters. The book is also punctuated by excerpts from Gajdusek's field journals from which the reader can gain, among other things, remarkable insight into the social customs of the region. One also has a graphic description of the geography and flora and also of the great difficulties encountered in trekking in this region. But not difficult enough to persuade Gajdusek to leave his typewriter behind.

I am intrigued by the fact that Gajdusek undertook his first post-morten examination on a case of kuru at 2 a.m. in a native hut during a howling storm by lantern light. Subsequently he undertook numerous other post-mortems and no doubt colleagues in clinical medicine and in general pathology will be amused to hear that the neuropathologists would have preferred the brains to have been more carefully suspended in fixative since one of the specimens was rather flattened! And also could the neuropathologists have complete spinal cords, representative dorsal root ganglia and a few peripheral nerves—tissue that is hard enough to come by in this country, let alone from the bush of New Guinea. Klatzo did, however, suggest quite early in the investigations that the neuropathological abnormalities he identified did have some similarities with the cases described by Jakob and Creutzfeldt. As a member of a WHO group who has been waiting for some years to obtain brains from fatal cases of trypanosomiasis in East, Central and West Africa and is still waiting, I find it quite remarkable that Gajdusek working in the bush should have been able in the course of a few months to undertake so many post-mortem examinations with the provision of abundant material for various laboratory and histological studies—including brains fixed in trace metal-free formalin.

And so the studies went on, yet by June 1957 no one else had yet made the arduous journey to see kuru. Gajdusek, in contrast, had already trekked many miles, encountered numerous cases, treated many natives for miscellaneous diseases in the course of his visits and collected innumerable specimens of blood, CSF and urine (24-hour specimens!). One wonders how anyone could achieve so much in such a short time. One is intrigued to note that the professional film team could not get through to Gajdusek, although at that time he was travelling round the bush undeterred by terrain and weather, and that the *New England Journal of Medicine* declined accepting his first paper—one of the principal reasons seems to have been that 'authentically new diseases are infrequent and difficult to come by'.

As the year progresses the letters are punctuated by scientific and not-so-scientific speculation as to the ætiology of kuru. I cannot really summarize the wealth of information contained in the letters but I did note that Gajdusek on his return from a patrol of some 1,500 miles observed that the Fore people were well nourished and that he had not found a single sign of dietary insufficiency. It is at least inferred that kuru was not caused by something that those afflicted with the disease had eaten!

This is not, nor was it intended to be, a scholarly review. If, however, it tempts people to read this book I shall be more than satisfied. Even for people without a particularly keen interest in kuru, it is fascinating and interesting reading.

HUME ADAMS

Neurosecretion and Brain Peptides: Implications for Brain Functions and Neurological Disease. (Advances in Biochemical Psychopharmacology, Volume 28). Edited by Joseph B. Martin, Seymour Reichlin and Katherine L. Bick. 1981. Pp. 727. New York: Raven Press. Price $88.40.

The publication of yet another symposium on brain peptides may cause dismay to scientists or doctors who want to keep up with progress in our knowledge but are overwhelmed by the exponential increase in literature in general, and of reports on congresses and conferences in particular. However, progress in the field of peptides has been so surprising and explosive, that it is probably only through reading reports such as this publication that one can remain informed. Not that much of what is discussed by the 112 contributors in 56 chapters has not been said elsewhere before. Yet new findings and new interpretations abound, and a few of these will follow here since they happened to strike the reviewer as interesting. The object of the conference was to sound how far present-day knowledge of polypeptides can help the understanding of neurophysiology and of pathogenesis and manifestation of nervous disease.

In Section 1 we are reminded that diabetes incipidus has long ago been recognized as due to the lack of the peptide vasopressin, made in hypothalamic nuclei and stored in the posterior lobe. However, the new surprise is the occurrence of vasopressin, bound to its 'carrier' neurophysin, in fibres which course from the paraventricular and other nuclei into distant parts of the brain and cord. The author's final comment is an understatement: 'the physiological significance of these new peptidergic pathways is not entirely clear at present'. The next speaker makes a similar comment, which characterizes the relative backwardness of our physiological knowledge by pointing out that our detailed biochemical information far exceeds any understanding of the physiological meaning of the biochemical processes. His article, however, shows great progress in physiological insight in some problems of protein synthesis. These would be unintelligible without the assumption that directional transport of each of the proteins is achieved by 'signalling' groups which enable the protein to move into the position where its function is to take place. What is true of proteins is, of course, valid for the familiar opioid peptides which are the concern of a number of articles throughout the book.

No book on biologically active substances could omit dealing with receptors recognizing these substances. Although most diseases known to be caused by receptor failures are endocrinological, myasthenia gravis attacks the neuromuscular junction, and the possibility that malfunction of the CNS could be caused by abnormal behaviour of receptors is an intriguing suggestion.

Substance P, discovered in 1931 but remaining elusive because peptide chemistry was not sufficiently advanced to obtain a pure substance, has aroused great interest since Leeman and her colleagues determined its sequence. Its presence in small diameter afferent pain fibres and spinal ganglia suggests its importance in pain perception, but its presence in many pathways within the brain, often together with substances which are well-established transmitters, opens up a new field of explaining and, we hope, combating pain.

Several presentations are devoted to the role of endogenous opioid peptides in analgesia. Other sections are concerned with physiological or clinical implications of progress in peptide biochemistry and localization. Growth, formation of CSF and blood-brain barrier are under the influence of peptides. It must, however, be admitted that in many of these subjects, speculation far outweighs solid knowledge. With regard to homeostatic phenomena such as thirst, food intake, body temperature and blood pressure, the role of peptides is better founded.

The last two sections deal with the possibility of a role for peptides in human disease. This is a field of great expectation, and there are some promising preliminary results. A group from the three Scandinavian countries has analysed urine samples of patients suffering from schizophrenia or autism, and found peptide excretion patterns different from those of control subjects. They suggest that a deficiency in some key-peptidases might be the underlying cause. It will be most interesting to see whether this hypothesis will stand the test of time.

M. VOGT

BRAIN

A JOURNAL OF NEUROLOGY

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A Journal of Neurology

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VOLUME CIV

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OXFORD
AT THE CLARENDON PRESS

1981

Oxford University Press, Walton Street, Oxford OX2 6DP
London Glasgow New York Toronto
Delhi Bombay Calcutta Madras Karachi
Kuala Lumpur Singapore Hong Kong Tokyo
Nairobi Dar es Salaam Cape Town
Melbourne Auckland
and associates in
Beirut Berlin Ibadan Mexico City Nicosia

© *Oxford University Press 1981*

Printed in Great Britain
at the University Press, Oxford
by Eric Buckley
Printer to the University

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BY ERIC BUCKLEY, PRINTER TO THE UNIVERSITY